

UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF MASSACHUSETTS

JOHN HANCOCK LIFE INSURANCE
COMPANY, JOHN HANCOCK
VARIABLE LIFE INSURANCE
COMPANY and MANULIFE
INSURANCE COMPANY,

Plaintiffs,

v.

ABBOTT LABORATORIES,

Defendant.

CIVIL ACTION NO. 05-11150-DPW

AFFIDAVIT OF CAROL SUSAN MEYER

I, Carol Susan Meyer, hereby declare and say:

1. I am over 18 years of age, and suffer from no condition or disability that would impair my ability to give sworn testimony. This affidavit is based upon my own personal knowledge.

Education and Professional Background

2. I am currently employed by Takeda Pharmaceuticals as a senior director in Project Planning and Management in the Global Research and Development division. From 1982 until October 2004, I was employed by Abbott Laboratories ("Abbott").

3. I received a Bachelor's Degree in psychology from Bethel College in St. Paul, Minnesota in 1980.

4. I began working at Abbott Laboratories ("Abbott") in 1982. From January 1999 to January 2000, I was the operations manager for the Anti-Infective Venture. In January 2000, I was promoted to senior operations manager for the Anti-Infective Venture. My responsibilities remained substantially the same as they had been in my previous position. In November 2002, I was promoted to Director of Global Clinical Operations, the position in which I remained until I left Abbott in 2004. As Director of Global Clinical Operations I was responsible for overseeing the execution of clinical trials in 22 countries.

Responsibilities as Operations Manager and Senior Operations Manager of Abbott's Anti-Infective Venture

5. When I became the Operations Manager of the Anti-Infective Venture in January 1999, the venture had two compounds under development: (1) ABT-773, a ketolide antibiotic; and (2) ABT-492, a quinolone antibiotic. It was my responsibility as the operations manager, and later as the senior operations manager, to oversee the operations of the ABT-773 development program. I was not responsible for ABT-492 although I did provide some mentoring to the operations manager for that compound.

6. Among other things, my responsibilities for ABT-773 included: timing, budgeting, organizing and preparing agendas for meetings, ensuring that agenda items were discussed, following up on issues that arose during the course of the development of the compound, and generally being the central point of contact on the operational execution of the project. I attended most, if not all, of the ABT-773 development team meetings through the life of the program, as well as several presentations regarding the compound given to Abbott's executives, including the Pharmaceutical Executive Committee ("PEC").

7. Dr. Carl Craft was the head of the Anti-Infective Venture when I started as operations manager for the venture. I reported directly to Dr. Craft until late March or early April 2001 when Dr. Stanley Bukofzer took over as head of the Anti-Infective Venture. When Dr. Bukofzer officially took over as venture head I met with him extensively to bring him up to speed on the development of ABT-773. Other members of the ABT-773 development team included Dr. Linda Swanson, at that time the director of the ABT-773 clinical research team to whom the project managers reported, and Dr. Joaquin Valdes, who eventually was the Medical Director of the ABT-773 development team. When Dr. Swanson retired, I took over responsibility for the ABT-773 clinical research team. I reported directly to Dr. Bukofzer when he replaced Dr. Craft as head of the Anti-Infective Venture.

8. There were other individuals involved with the ABT-773 project who were not part of the Anti-Infective Venture, including Jeanne Fox and Greg Bosco, who were the individuals responsible for regulatory issues related to ABT-773, and Rod Mittag, who was a new product planning member and dealt with the commercial aspects of the compound.

9. My responsibilities as the operations manager of the Anti-Infective Venture also included drafting the Monthly Status Project Reports for ABT-773 with input from the other team members. As an example of such reports, attached hereto as D's Exhibit 613 is a true and correct copy of the March 2001 Monthly Project Status Reports for ABT-773 that I drafted.

There Was No Evidence of QT Prolongation Issues With ABT-773 as of March 2001

10. Since ABT-773 was an anti-infective, I was aware at the outset of its development that there were hurdles to approval by the FDA because of the broad population that is treated by anti-infectives. The majority of patients who are treated with anti-infectives have respiratory tract infections but are otherwise healthy; they generally do not have a major underlying disease. Therefore, the FDA requires that the drugs be extremely safe and effective.

11. I was aware, as were other individuals on the ABT-773 development team, that macrolide anti-infectives have been well known for years to potentially have QT prolongation effects at high doses, in some circumstances. I was also aware that since ketolides are a class of compounds related to macrolides, the FDA was paying attention to this class of compounds with regard to QT issues. I was also aware, as was the entire pharmaceutical industry at that time, that the FDA had concerns about the potential for cardiac events with regard to all new drugs, and anti-infectives in particular.

12. In or around June 1999, I drafted, with input from the ABT-773 development team, the ABT-773 Development Plan. Attached hereto as D's Exhibit 608 at ABBT204960-5041 is a true and correct copy of the ABT-773 Development Plan. As noted in the Development Plan, as of June 1999, the current clinical data that we had observed to that point indicated "no evidence of QTc prolongation." *Id.* at ABBT204965. We also had determined that ABT-773 was similar to "clarithromycin and erythromycin in its effects on QT intervals in preclinical data." *Id.* Clarithromycin and erythromycin are two anti-infectives that had already been approved and successfully marketed.

13. Since Dr. Jeffrey Leiden had only recently joined Abbott, in December 2000, the ABT-773 development team gave an overview presentation regarding ABT-773 to him. I attended the ABT-773 project review meeting with Dr. Leiden and helped to prepare the slides that were presented. Attached hereto as D's Exhibit 608 at ABBT20588-ABBT205256 is a true and correct copy of the December 2000 presentation for ABT-773 that I attended. I also presented the sections of the presentation regarding the I.V. formulation and the Japan program. As noted in the presentation, we had not observed a consistent QT effect during the Phase IIb clinical trials. *Id.* at ABBT205202. The only QT prolongation effect we observed was during Phase I studies for doses greater than 800 mg, a dose far higher than we planned to prescribe to patients. The development team had concluded that the ABT-773 clinical trial data to date did not demonstrate a QT prolongation issue but that additional work would need to be done to demonstrate this point to the FDA. At that time, we were taking every precaution to ensure that we would have sufficient data to meet the FDA's expectations with regard to this issue. For example, by adding EKG monitoring in Phase III, we felt we were obtaining data above and beyond what would be required to satisfy the Agency's concerns.

14. On February 12, 2001, I helped to prepare and attended an update presentation on the ABT-773 program for the Pharmaceutical Executive Committee ("PEC"), the senior management group at Abbott which oversaw the research and development teams at Abbott. Attached hereto as D's Exhibit 608 at ABBT205047-87 is a true and correct copy of the presentation slides for that meeting that I helped prepare. In conjunction with this meeting, I drafted, with input from the development team, a

shorter talking points memo that contained a summary of the information provided during the presentation. Attached hereto as D's Exhibit 608 at ABBT205042-46 is a true and correct copy of the ABT-773 Update February 12, 2001 summary that I drafted. As reflected in both of these documents, as of February 12, 2001, we had not observed a QT prolongation issue with ABT-773 at the doses at which the drug would be prescribed to patients. *Id.* at ABBT205043 & ABBT205061. We recognized that ABT-773 "would be presumed guilty until proven innocent" with regard to QT prolongation issues because that was the case with almost every safety issue presented to the FDA, but our concern was no higher than it would have been with the development of any other anti-infective. *Id.* at ABBT205043.

15. From March 7-9, 2001, after the acquisition of Knoll Pharmaceuticals, Abbott held an off-site Portfolio Review Meeting to discuss the compounds that Abbott had under development at the time as well as the new compounds that were acquired through the acquisition. I did not attend this Portfolio Review Meeting, but I helped to create the slides that Dr. Carl Craft used for the ABT-773 presentation he gave at the meeting. Attached hereto as D's Exhibit 622 is a true and correct copy of the slides that I helped create for Dr. Craft's presentation during the March 2001 Portfolio Review Meeting. As reflected in the slides, as of early March 2001, the ABT-773 development team was aware that there was a possibility that the FDA would require class QT prolongation labeling for ABT-773, since the compound was a member of the ketolide class of anti-infectives and related to the macrolide class of anti-infectives. *Id.* at ABBT0013212. However, as of early March 2001, we did not have evidence of a QT prolongation issue with ABT-773 itself at the doses it would be prescribed to patients.

Our action items on this issue were to continue to conduct EKG monitoring in our Phase III trials, to conduct the additional dog toxicity trial requested by the FDA, and to conduct a Phase I trial later that year in cardiac impaired patients to demonstrate that ABT-773 was clear of QT prolongation issues. *Id.* at ABBT0013213.

16. Later in March 2001, I helped to prepare a follow-up presentation on ABT-773 for a meeting with the PEC. Attached hereto as D's Exhibit 631 is a true and correct copy of the March 19, 2001 presentation slides I helped to create. As reflected in the presentation slides, the status of ABT-773 with regard to QT prolongation was unchanged from the earlier December and February reviews of the compound. *Id.* at ABBT120480.UR.

17. As reflected in the Monthly Status Project Report that I created at the end of March 2001, there were "[r]egulatory uncertainties over how to deal with the ketolide/macrolide class regarding QT interval effects" and we were developing a "QT strategy" regarding an additional Phase I clinical trial to be finalized in April 2001. D's Exhibit 613 at ABBT0000431. Our focus on QT prolongation was driven by the FDA's concern with QT issues for all anti-infectives. Based on my discussions with fellow members of the ABT-773 development team and on all the other information available to me, I did not believe, as of March 2001, that ABT-773 had an issue with QT prolongation that would prevent its approval by the FDA.

As of March 2001 ABT-773 Did Not Have a Hepatotoxicity Problem

18. Throughout my work in the Anti-Infective Venture I was aware that the FDA was generally concerned with hepatotoxicity or liver toxicity issues with regard to new drugs that were being submitted for regulatory approval. As noted in the June 1999

ABT-773 Development Plan that I drafted, and which is discussed above, we had observed elevated liver enzymes in a small number of Japanese volunteers in a single Phase I study. D's Exhibit 608 at ABBT204965. The study had included Japanese patients living in Hawaii. I became aware during that study and after its completion that there were a few patients who demonstrated elevated liver function tests ("LFTs") during the study. I was involved in discussions with the development team after the results of that study became available during which it was recommended that we repeat the study based on a concern that the unusual LFT results were due to the high fat diet of some of the study patients, rather than anything to do with ABT-773. The clinical trial was repeated in Japan and we determined that the initial study results were an anomaly. Attached hereto as D's Exhibit 587 at ABBT0000302-308 is a true and correct copy of the January 2001 ABT-773 Monthly Project Status Report that I drafted for ABT-773.

As reflected in the document:

The Japan Phase I Dose-Ranging study was completed in February [2001] and drug analysis is ongoing. No increases were seen in ALT/AST, with all values within the normal range. Based on these results, ***ABT-773 is clear in terms of hepatotoxicity profile*** and the liver enzyme abnormality observed in Hawaiian Phase I with Japanese population was seen as a result of the high fat diet during the study period.

Id. at ABBT0000304 (emphasis added).

19. We had concluded in January 2001 that there were no liver toxicity issues with ABT-773. We did not see any clinical results that caused us to change that assessment through the spring and summer of 2001. For example, the February 12, 2001 update summary document that I created notes the FDA's concerns with liver toxicity but notes that the results of the repeat Japanese study "showed no evidence of any problem with LFTs in the Japanese or Caucasians." D's Exhibit 606 at ABBT205044. The March

19, 2001 presentation similarly notes the repeat study and the fact that there was no evidence of LFT increases in Japanese or Caucasian patients. D's Exhibit 631 at ABBT120481.UR.

20. The development team did not have any indication of a potential liver toxicity issue with ABT-773 until the fall of 2001, when we observed unexpected LFTs during an additional Phase I study for QT prolongation that began in October 2001. Attached hereto as D's Exhibit 789 is a true and correct copy of the October 2001 Monthly Status Project Report for ABT-773 that I drafted. As noted in the report, "the Phase I QT Study, M01-325, was put on hold at the 2nd dosing period to allow for analysis of liver elevations seen in 4 subjects." *Id.* at ABBT0000727. The elevated LFTs observed during the M01-325 study were unexpected given our earlier determination that ABT-773 did not have potential liver toxicity issues.

The Dosing of ABT-773

21. Phase II trials are generally dose-ranging trials to determine the dose at which the drug will be prescribed. As of June 1999, we had decided as a result of Phase II trials for ABT-773 that the drug would be dosed with 150 mg tablets at either QD or BID dosing, depending on the severity of the indication. We were planning to conduct several Phase III trials in late 2000 and 2001 to determine whether the daily dosing would be once or twice a day.

22. As reflected in the June 1999 ABT-773 Development Plan that I created, the development team had determined that ABT-773 would be developed for once-a-day ("QD") dosing for the two less severe indications for which it was being developed, chronic bronchitis and pharyngitis. *See* D's Exhibit 608 at ABBT204964. It was unclear

as of June 1999, when I drafted the Development Plan, whether we would be able to file for QD dosing for the two more severe indications, community-acquired pneumonia (“CAP”) and acute bacterial or maxillary sinusitis (“sinusitis”). *Id.* Since the largest market share for ABT-773 was bronchitis, it was important to have once-a-day dosing for that indication. CAP and sinusitis were much smaller indications and I understood, based on discussions with other members of the ABT-773 team, including Rod Mittag, that the commercial impact of twice-a-day dosing for those indications was much smaller than for the larger, less severe indications of pharyngitis and bronchitis.

23. As reflected in the February 2001 presentation discussed above that was given to the PEC, we were conducting Phase III comparator trials during the spring and summer of 2001 to determine whether we would be able to develop ABT-773 with QD dosing for all indications. D’s Exhibit 608 at ABBT205069.

24. As noted in the March 7-9, 2001 Portfolio Review Meeting presentation discussed above, “[a] dose decision of 150 mg QD vs 150 mg BID in CAP and sinusitis [was to be] made based on Phase III data by July 2001.” D’s Exhibit 622 at ABBT0013214. The presentation also reflects that we had already decided that we would be able to dose the less severe indications of pharyngitis and chronic bronchitis once-a-day. *Id.* at ABBT0013210.

25. I participated in drafting the slides for a July 25, 2001 decision analysis presentation to Dr. Leiden and Dr. Leonard regarding the dosing of ABT-773. Attached hereto as D’s Exhibit 788 is a true and correct copy of the ABT-773 Dosing Options presentation that I helped to draft and was given to Dr. Leiden and Dr. Leonard on July 25, 2001. As noted in the presentation, due to the fact that our Phase III trials comparing

QD and BID dosing were not complete as of July 2001, our options in late July were either to wait for the conclusion of those trials to determine whether we could move forward with QD dosing for the CAP and sinusitis indications, or to proceed immediately with BID dosing for those indications. *Id.* at ABBT119373.UR-ABBT119384.UR. It was the development team's recommendation that proceeding immediately with BID dosing for the more severe indications of CAP and sinusitis was preferable from a commercial and regulatory perspective so as to not delay the development of the compound. *Id.* at ABBT119382.UR. We also knew that we would potentially be able to launch the compound with QD dosing for all of the indications, including CAP and sinusitis, after the initial launch if such dosing received regulatory approval.

The Pediatric Program

26. As noted in the December 2000 presentation on ABT-773 discussed above, the Pediatric Program for ABT-773 had been initiated in January 2000. D's Exhibit 608 at ABBT205238. In September 2000, we conducted our first taste evaluations of the compound and found that the formulation was too bitter and needed to be reformulated. During December 2000, the development team for ABT-773 proposed developing a new formulation for the pediatric program with a Go/No Go decision in June 2001. Since the tablet formulation was the main focus of the development team, the development team decided to delay the oral suspension formulation project until the Phase III clinical trials were underway.

27. Therefore, as of March 2001, the pediatric program for ABT-773 was on hold until the oral suspension formulation could be developed. The development team intended to develop a pediatric formulation as part of our overall development plan for

ABT-773, but we were also aware, based on information provided by Abbott's Regulatory Affairs department, that we could seek a waiver or deferral of the requirements of the FDA's pediatric rule.

28. Information regarding the pediatric program was provided to Dr. Leiden and Dr. Leonard at the Decision Analysis presentation on July 25, 2001, discussed above. D's Exhibit 788 at ABBT119409.UR-ABBT119414.UR. As noted in the presentation, we had two or three new formulations under development and expected to continue to work on the pediatric program later that year. *Id.*

The April 2001 Ketek Advisory Committee Meeting

29. In April 2001, the FDA held its first advisory committee meeting for Ketek, a ketolide that was under development by Aventis, another pharmaceutical company, and was at a more advanced stage of development than any other ketolide. I watched the Ketek advisory committee meeting via satellite with other members of the ABT-773 development team, including Dr. Bukofzer, at Abbott. We had expected that the Ketek advisory would be related to efficacy concerns since there were so many efficacious anti-infectives already on the market. As reflected in the February 12, 2001 presentation, we did not expect the Ketek advisory meeting to be related to the FDA's QT concerns. D's Exhibit 608 at ABBT205060. In fact, the Ketek advisory focused very heavily on the size of Ketek's safety database for both QT prolongation and liver toxicity, as well as on efficacy. As noted in the July 25, 2001 decision analysis presentation to Drs. Leiden and Leonard, discussed above, "the [i]mpact of the Ketek advisory on the ABT-773 clinical development program" was an "increase in program size to satisfy safety database and resistance claim requirement." D's Exhibit 788 at ABBT119364.UR.

We understood that the Ketek advisory “defined new regulatory standards” for anti-infectives. *Id.* at ABBT119366.UR.

30. Specifically, the Ketek advisory made it clear to us that the FDA would require many more patients in clinical trials for ABT-773 and other ketolides to demonstrate that there were no QT prolongation or liver toxicity issues with the compound. The unexpected elevated liver function tests that we saw in the October 2001 clinical trial that I described above, were seen as significant because of the Ketek advisory. Based on our analysis of the impact of the meaning of the Ketek advisory for all anti-infectives in development, we knew that the FDA would require significantly larger safety databases for compounds that had even a small number of patients with potential liver or QT prolongation issues. We realized in April 2001 that the development of ABT-773 would be much more expensive and would take even more time than we had previously believed.

31. Moreover, while we had expected that we would be able to support our resistance claim for ABT-773, the Ketek advisory made that hurdle much more difficult. Part of the target product profile for ABT-773 was a label that ABT-773 was effective against resistant pathogens. Resistant pathogens are pathogens that are resistant to other anti-infectives such as penicillin and macrolides. We had hoped that at the End of Phase II meeting, the FDA would confirm the number of bacterial samples resistant to penicillin or macrolides (also referred to as “isolates”) that would be needed to support our resistance claim, but the FDA did not do so. The number of isolates was important because it would determine the size of our clinical trials. The FDA’s April 2001 Ketek advisory made it clear that the number of isolates that Ketek had presented had not been

sufficient and that much more clinical trial data would be required to support Ketek's resistance claim. We concluded, as a result of our analysis of the meaning for ABT-773 of the Ketek advisory committee's actions and comments with regard to Ketek's resistance claim, that we would have to increase substantially the number of resistant isolates we had planned to obtain for the ABT-773 resistance claim. In order to obtain a larger number of isolates, we would have to expand the number of patients in our trials, thus increasing both time and expense. While we knew that ABT-773 had excellent activity against penicillin and macrolide resistant pathogens *in vitro*, there were not that many patients with bacterial infections that were resistant to anti-infectives, so obtaining clinical trial data to demonstrate that ABT-773 would work against resistant pathogens was already a difficult process. The FDA's Ketek advisory made obtaining this resistance claim even more difficult.

The Discontinuation of ABT-773

32. In December 2001, I was informed that there had been a decision made by the PEC that there would be no new studies or activities for ABT-773. Ongoing clinical studies and activities, however, were to continue. Throughout the winter of 2001 and the spring of 2002 there was at least one ongoing clinical trial. Attached hereto as D's Exhibit 790 is a true and correct copy of the March 2002 Monthly Status Project Report for ABT-773 that I created. As noted in the report, as of March 2002, the Phase I QT Study that had been previously put on hold was re-started in March and another Phase III study was ongoing. *Id.* at ABBT0000963.

33. Eventually, in the summer of 2002, a decision was made by Abbott's management to discontinue the development of ABT-773 and to out-license the

compound. Before I left Abbott in 2004 I was involved in the effort to out-license ABT-773. I later learned that Abbott had successfully out-licensed ABT-773 to Advanced Life Sciences.

I declare under penalty of perjury under the laws of the United States of America that the foregoing is true and correct.

Executed on 15 Feb, 2008 at Deerfield, IL

Carol Susan Meyer
Carol Susan Meyer

January 2001

ABT-773 Project Status Report

Monthly Highlights

- We sent responses to the FDA based on their written comments from the end of Phase II meeting on Dec 14th and have only received feedback on the CAP protocol. We have implemented all requested changes for the other 3 indications and have IRB approved amendments. We have also re-submitted to European ethics committees and MOHs were required.
- All Phase III U.S. studies are actively enrolling patients. European studies will start enrollment this month, as we have initial approvals in at least one country for each protocol.
- Plans are in place to initiate sites in Central America, So Africa and So America for CAP and ABS for their winter seasons starting in June. This will enable us to continue enrolling once the season in the Northern Hemisphere comes to a close and will help to insure that we obtain sufficient patients to make a dose selection for these 2 indications.
- A decision on funding for the IV formulation is required in February to initiate the first Phase I study by April 2nd. This study will enable us to determine the appropriate IV dose and evaluate injection site pain with the formulation prior to a Multiple Dose study. Timing for Phase I Go/No Go by September is critical if we would like to have an IV filing within a year of the tablet filing.
- The Japan Phase I Dose-Ranging study was completed in February and drug analysis is ongoing. No increases were seen in ALT/AST, with all values within the normal range. Based on these results, ABT-773 is clear in terms of hepatotoxicity profile and the liver enzyme abnormality observed in Hawaiian Ph I with Japanese population was seen as a result of the high fat diet during the study period.

| Key Progress Gauges - January Accomplishments | | Target Date | Status |
|--------------------------------------------------------------------------------------------------------------------------|--|--------------------|--------------------------------------|
| Complete End of Phase II CMC/BioPharm package to request meeting with FDA. | | 01/31 | To be completed by 2/16 |
| Complete Phase III protocol amendments and re-submit to European Ethics committees. | | 01/31 | Complete |
| Complete manufacture of final NDA formulation lots. | | 01/31 | Complete |
| Make a pediatric strategy recommendation based on team review of pediatric data from formulation, PK, taste evaluations. | | 01/31 | Strategy meeting scheduled for 2/16. |
| Complete pilot scale activities in IDC for the U.K. manufacturing site. | | 01/31 | Complete |
| February Projections | | Target Date | Status |
| Initiate enrollment in European Phase III studies. | | 02/19 | |
| Initiate commercial scale process development for the US formulation. | | 02/12 | |
| Deliver bulk drug campaigns 14 and 15. | | 02/16 | |
| Initiate NDA stability of final NDA formulation lots. | | 02/06 | |
| Submit Phase III comparative CAP & ABS protocols for CRO bids to initiate these studies in 4 th Q 2001. | | 02/28 | |
| Finalize BAL protocol for Japan to initiate in April. | | 02/28 | |

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January 2001
ABT-773 Project Status Report

Key Issues/Decisions/Events

| Area | Issue/Decision/Event | Progress |
|-------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| SPD/PARD | A change in bulk drug physical or chemical properties during formulation development will result in a delay in the Aug 2002 filing date. If at the 1200L scale, a delay of up to 18 months. | A strategy for the bulk drug lots that will be used in the NDA formulation runs will be reviewed with the CMC Technical Committee in early December. Bulk drug properties and granulation variables are being evaluated as a means to develop appropriate physical specifications for the bulk drug. |
| Regulatory | An end of of Phase II meeting with FDA was targeted for the end of September/mid October timeframe, but rescheduled to the end of November at the request of FDA. | Meeting with FDA was held on November 27 th . QT effects are the current hot topic for the FDA, and was reflected in the changes they requested to the Phase III program. They also requested an acute tox study in dog to further evaluate cardiac effects. The required "body of evidence" for obtaining a resistance claim for <i>s.pneumo</i> was discussed and the FDA recommendation included having an IV formulation to get bacteremic patients and more serious CAP infections. Protocol amendments have been signed off incorporating all FDA requested changes and implemented in the U.S. and Europe. |
| Regulatory | Regulatory uncertainties over how to deal with the ketolide/macrolide class regarding QT interval effects. | FDA concern is whether ketolides behave like macrolides and whether there may be a class effect. They also discussed whether a Phase I study should be conducted in subjects with underlying cardiac disease. ECG monitoring will be done in all Phase III studies with the exception of the ASP study in Europe. |
| SPD | Definition of starting materials for the bulk drug (at what step in the manufacturing process) will affect our ability to continue with process improvements necessary to continue to reduce the cost of the bulk drug. This has cost implications up to 3 years post-launch. | The End of Phase II CMC meeting with FDA will be requested for January 2001 to present the package on starting material definition for step 5 intermediate. Meeting is targeted for the end of March. |
| Venture/NPD | The pharmacokinetic profile does not meet the preconceived ideas of some PK/PD experts. Because of this, the 150mg QD dose may be challenged. | Phase IIb studies indicated efficacy with 150 mg daily dose in ABECB and ABS. PK/PD data together with ribosome kinetics support the decision to proceed with 150mg QD in mild infections (ABECB and ASP) and select between 150mg BID and 150mg QD in CAP and ABS. Recent PK/PD data support AUC of 1-6 for clinical exposure in CAP necessary for cure. Phase IIIa studies to be complete by 5/2001 to decide the dose requirements for CAP and ABS. To address this issue and potentially create a new model for evaluating PK/PD, internal efforts to characterize ribosome binding properties are ongoing by Discovery, with an advisory planned with external experts June-July 2001 to define further study. |
| NPD | Phase IIIa data will be important predictors of commercial value of compound (QD vs BID dosing for CAP/Sinusitis, efficacy, adverse event rates. | Phase IIIa studies to be complete 5/2001. FDA changes to the Phase III protocols creates a challenge for us to still meet the Go/No Go decision for the QD vs BID dose for CAP and ABS by June. The team is working to overcome the challenges as much as possible. |

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January 2001
ABT-773 Project Status Report

| Area | Issue/Decision/Event | Progress |
|----------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Venture | Obtain sufficient quantity of clinical isolates with resistant organisms to request a separate claim for activity against resistant <i>S. pneumoniae</i> . | FDA feedback regarding a resistance claim for PRSP is that a sufficient "body of evidence" needs to be gathered to convince them to grant a claim. They estimate >10 resistance isolates will be required, CAP and ABECB isolate requirements need further clarification, but ABS isolates are evaluated separately. They are not convinced about the clinical significance of MRSP and need further evidence. They suggest that an IV formulation to obtain bacteremic patients and more severe CAP infections will enhance the probability of obtaining the claim. |
| Clinical | The Phase II clinical program is large, intense, and must be conducted successfully in a relatively short period of time. | FDA requested changes are being assessed for protocol amendments. The subject Informed Consent revisions were submitted to central IRBs and approval was obtained by Dec. 8 th . No FDA feedback was received on our responses to the End of Phase II meeting for ABS, ABECB or ASP protocols. We have incorporated all requested changes and submitted to IRBs in the U.S. and Ethics Committees/MOHs in Europe. European study enrollments expected to start in mid-February. We are working to start countries in the So Hemisphere to compensate for the delays. |
| Japan | Due to the dose change in the base development program, Phase I will be repeated in Japan to further evaluate dose-ranging. An increase in liver enzymes was observed in the low and medium dose groups of Japanese volunteers in the first study in Hawaii, and will be further evaluated in the Phase I studies done in Japan. A Japanese dose and formulation, as well as the Phase II/III studies, will be defined once the dose-ranging has been completed. This plan will determine the filing date for Japan. | The Japan Phase I Dose-Ranging study was completed in February and drug analysis is ongoing. No increases were seen in ALT/AST, with all values within the normal range. Based on these results, ABT-773 is clear in terms of hepatotoxicity profile and the liver enzyme abnormality observed in Hawaiian Ph I with Japanese population was seen as a result of the high fat diet during the study period. The Japanese BAL study will start in April. Dose selection and BAL results need to be available prior to a meeting with Kiko to discuss the Phase II/III strategy. |
| HPD | The initial development of an IV formulation has been completed and clinical supplies have been manufactured by HPD. Year 2001 funding was committed by HPD. | HPD funding for 2001 (\$7MM) is no longer approved. At the ABT-773 Portfolio meeting, Jeff Leiden committed to find funding (approx. \$1MM) to do the Phase I studies for the IV in 2001 to enable us to evaluate the viability of the formulation in terms of pain on injection and the dose requirements. Need confirmation on funding availability in February to initiate Phase I in April. |

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January 2001
ABT-773 Project Status Report

| Project Cost Summary - January | | | | | | |
|--------------------------------|----------------------------|---------------|-----------------------|----------------------------|----------|----------------------|
| \$000's Activity | Cumulative through 2000 | YTD Actual | Projected Year-end | Current Funded Year-end | Variance | Cumulative to NDA |
| Clinical Program | 46.5 | 6.6 | 61.7 | 61.7 | ... | 136.4 |
| CMC (PAR, SPD & IDC) | 77.9 | 1.4 | 21.7 | 21.7 | ... | 110.5 |
| Drug Safety | 9.0 | .1 | 1.9 | 1.9 | ... | 11.7 |
| Other Support Costs | 20.4 | .3 | 2.7 | 2.7 | ... | 29.1 |
| Total | 153.8 | 8.4 | 88.0 | 88.0 | ... | 287.7 * |

Tablet NDA = 8/2002; IV Formulation unfunded; Pediatric Formulation unfunded.

* Cumulative cost to NDA based on 3Q 2002 filing.

| Clinical Study Progress | | | | | | |
|-------------------------------------------------------|------------------------------------------|----------------------------|----------------------|--------------------------|-----------------------|--|
| Protocol # - Study Name | Start (1 st Patient Dosed) | End (Last CRF In House) | Total R/OSS \$000 | Total Target Patients | Current Enrollment | |
| M99-048, Phase II Dose Ranging, ABECB | 9/1/99 | 3/31/00 | 3,885 | 300 | 384 | |
| M99-053, Phase II Dose Ranging, Sinusitis | 9/1/99 | 4/30/00 | 3,172 | 300 | 292 | |
| M99-054, Phase II Dose Ranging CAP | 9/1/99 | 4/30/00 | 4,089 | 300 | 187 | |
| M00-219 Phase III CAP, Dose Ranging | 11/7/00 | 4/30/01 | 14,400 | 800 | 68 | |
| M00-216 Phase III ABECB vs Azithromycin | 11/7/00 | 4/30/01 | 7,381 | 600 | 125 | |
| M00-217 Phase III ABECB vs Levofloxacin | 11/7/00 | 4/30/01 | 4,600 | 500 | 0 | |
| M00-225 Phase III Sinusitis Dose Ranging | 11/7/00 | 4/30/01 | 7,200 | 600 | 126 | |
| M00-223 Phase III Pharyngitis vs Penicillin 250mg TID | 11/7/00 | 4/30/01 | 4,340 | 520 | 161 | |
| M00-222 Phase III Pharyngitis vs Penicillin 500mg TID | 11/7/00 | 4/30/01 | 5,000 | 520 | 0 | |

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January 2001
ABT-773 Project Status Report

Business Rationale

Date: January 2001
Acquired:
Franchise: Anti-infective
Venture: Anti-infective

ABT #: ABT-773
Trade & Generic Name: TBD, TBD
Mechanism of Action: Ketolide, antimicrobial

Indications: Acute Exacerbations of Chronic Bronchitis, Community

Pneumonia, Pharyngitis, Acute Maxillary Sinusitis

Product Profile

| Attribute | Date Defined | Probability* | Confirm Status | Share Impact |
|-------------------------------------------------------------------------------------------------|--------------|--------------|----------------|--------------|
| Activity against Gram +, Gram -, atypicals | 3/1997 | High | Confirmed | High |
| Activity against <i>H. influenzae</i> = azi | 3/1997 | High | Confirmed | High |
| Active against 80% of Gram + resistant strains of efflux and M.S.-c | 3/1997 | High | Confirmed | High |
| Active against most macrolide resistant pathogens on a bacterial-worldwide-susceptibility panel | 3/1997 | High | Confirmed | High |
| Incidence of GI side effects=azi | 3/1997 | Low | Not Met | High |
| Incidence of drug-interactions = clari, no contraindications | 3/1997 | High | 6/2001 | Medium |
| QD dosing adult/label | 3/1997 | Medium | 6/2001 | High |
| QD dosing ped OS | 3/1997 | Medium | 9/2000 | Medium |
| QD dosing for IV | 3/1997 | Medium | 12/2000 | High |
| Comparable pain at injection site than azi | | Medium | 12/2000 | Low |
| Less metallic taste than clari XL | 3/1997 | Medium | 6/2001 | High |
| OS equal in taste to Azi, Omnicef | | Low | 9/2000 | High |
| 5-day therapy for most indications | 3/1997 | Low | 6/2000 | High |
| COGS > 80% SMM at launch | 3/1997 | High | 12/2001 | Low |
| Maintain balanced plasma/tissue levels similar to clari | | Medium | 12/2001 | Medium |

* Probability Key:
High = 70-100%
Medium = 30-69%
Low = 0-29%

Market Forecast

| | PCC/DDC 3/1997 | Revised 1/1999 | Current Revised 8/2000 Tab/Cap Only* |
|--------------------------------|--------------------|-------------------------------|--------------------------------------------|
| Patent Status: | 9/2016 | 9/2016 | 9/2016 |
| NDA Filing: | 12/2000(tab/cap) | 8/2002 (all) | 8/2002 (tab/cap) |
| Ex-U.S. Filings: | 9/2001(OS, IV) | 8/2002 (all) | 8/2002 (all) |
| Projected U.S. Launch: | 2/2000(tab/cap) | | |
| | 9/2001(OS, IV) | | |
| | 4/2002(tab/cap) | | |
| Projected 9x U.S. Launches: | 1/2003(OS, IV) | 9/2003 | 8/2003 |
| | 4/2002(tab/cap) | | |
| | 1/2003(OS, IV) | | |
| Peak TRx Share, U.S.: | 4.4%TC, 4.7%OS; | 4%TC, 4%OS; | 7.5% |
| | 3.3%IV | 10%IV | |
| Peak TRx Share, ex-U.S.: | N/A | 3.3%TC, N/A OS, IV | 4.4 to 6.9% |
| Peak Sales, U.S.: | \$428TC, \$118OS | \$399TC, \$58OS | \$432 |
| Peak Sales, ex-U.S.: | \$26IV | \$13.8IV | |
| (\$MM) | N/A | \$360TC, N/A OS, IV | \$386 |
| Post-Tax NPV @ 12.5%, U.S.: | N/A | \$200TC, (\$6.1)OS | \$297 |
| (\$MM) | | (\$1.1)IV | |
| (no clari cannibalization) | | (note: discount rate was 15%) | |
| Post-Tax NPV @ 12.5%, ex-U.S.: | N/A | \$240TC; | \$208 |
| (\$MM) | | N/A OS, IV | |
| (no clari cannibalization) | | (note: discount rate was 15%) | |
| Avg daily dose | | | 150mg QD |
| Target Drug Cost/kg at Launch | \$1163TC; \$2173OS | \$3633TC; \$291OS | \$3000 |
| SMM at Launch (U.S., Ex-U.S.) | \$3720IV | \$8953IV | |
| SMM at Year 5 (U.S., Ex-U.S.) | -- | 88%TC, 63%OS; 100%IV | 85%, 87% 90%, 93% |

* Includes Tab/Cap only. A development plan will be established for OS and IV programs.

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Project Overview

January 2001
ABT-773 Project Status Report

Metrics Dates

| Description | Date |
|---------------------------------------|---------|
| DDC Meeting | 3/1997 |
| Start of first GLP animal tox study | 6/1997 |
| First dose in human (beg. Phase I) | 12/1997 |
| First dose in patient (beg. Phase II) | 9/1999 |
| First dose in Phase III | 11/2000 |
| Last Patient/Last Visit | 4/2002 |
| NDA Filing | 8/2002 |
| NDA Approval | 8/2003 |
| Europe (EMEA) Filing | 8/2002 |
| Europe (EMEA) Approval | 8/2003 |
| Japan Filing | TBD |
| Japan Approval | TBD |

See the following page for a
summary of Bulk Drug
deliveries in SPD.

| PARD | | |
|------------------------------------------|-----------------|---------|
| Activity | Plan 12/1998 | Actual |
| Phase I Formulation (Caps)* | 12/1997 | 12/1997 |
| Phase II Formulation (Tablet) | 7/1999 | 8/1999 |
| Clinical Supplies Phase IIB | 7/1999 | 8/1999 |
| Phase III Formulation (Tablet) | 4/2000 | 7/2000 |
| Phase III Clinical Supplies Manufactured | 9/2000 | 9/2000 |
| NDA Lots (3) Completed | 7/2000 | 01/2001 |
| Completion of 1 Year Stability for NDA | 8/2001 | |
| Formulation Peer Review | 11/2001 | |

Toxicology

| Toxicology Activity | Plan Start 12/1998 | Actual Start Date | Report Completed |
|------------------------------|-----------------------|----------------------|---------------------|
| 2-week oral Rat/Monkey | 7/1997 | 6/1997 | 8/1998 |
| Acute Studies | 8/1997 | 8/1997 | 12/1997 |
| Mouse Lymphoma/Micronucleus | 11/1997 | 11/1997 | 4/1998 |
| 1 Month Rat/Monkey | 12/1997 | 12/1997 | 12/1998 |
| Pregnant Rat/Rabbit RF | 1/1998 | 1/1998 | 11/1998 |
| SEG II Rat/Rabbit | 3/1998 | 3/1998 | 2/1999 |
| Guinea pig sensitization | 11/1998 | 11/1998 | 2/1999 |
| 3 Month oral Rat/Monkey | 9/1999 | 10/8/1999 | 8/2000 |
| Seg I/III Rat | 9/1999 | 10/8/1999 | 12/2000 |
| IV Irritation studies, set 1 | 7/1999 | 7/15/1999 | 8/1999 |
| IV Irritation studies, set 2 | 2/2000 | 2/2000 | 3/2000 |
| IV 2-week Rat/Monkey Studies | 6/2000 | 6/2000 | 01/2001 |
| Neonatal/Juvenile Rat | 10/1999 | 11/1999 | 7/2000 |

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January 2001
ABT-773 Project Status Report

SPD ABT-773 Bulk Drug Deliveries Update

| | <u>Target Date</u> | <u>Amount</u> | <u>Delivery Date</u> | <u>Amount</u> | <u>Lot #</u> | <u>Amount after milling</u> |
|-----------------------|--------------------|---------------|----------------------|---------------|--------------|-----------------------------|
| Campaign 1 | 2/28/99 | 200 Kg | 2/23/99 | 209 Kg | 50-007-CA-00 | 207.5 Kg (2/26)* |
| Campaign 2a | 6/15/99 | 140 Kg | 6/17/99 | 131 Kg | 54-702-NI-00 | 129.4 Kg (6/19)* |
| Campaign 2b | 7/15/99 | 140 Kg | 7/21/99 | 121.5 Kg | 55-208-CB-00 | 119.3 Kg (8/4)* |
| Tox lot | 8/30/99 | 5 Kg | 8/25/99 | 6.1 Kg | 55-718-NI-00 | |
| Campaign 3a | 9/30/99 | 160 Kg | 10/8/99 | 170.5 Kg | 58493CB00 | 138.4 Kg (10/16)* |
| Campaign 3b | 10/21/99 | 160 Kg | 10/11/99 | 176.5 Kg | 58494CB00 | 169.5 Kg (10/16)* |
| Pilot run 1 | ----- | 15 Kg | 10/30/99 | 18.9 Kg | 59763N100 | no milling |
| Pilot run 2 | ----- | 15 Kg | 2/5/00 | 15.5 Kg | 61790NI00 | no milling |
| Pilot run 3 | ----- | 25 Kg | 1/30/00 | 27.5 Kg | 62764CB00 | 27.3 Kg (4/18)* |
| Campaign 4 | 12/10/99 | 320 Kg | 11/23/99 | 355 Kg | 61741CB00 | 309 Kg (3/2)* |
| Campaign 5 | 12/30/99 | 300 Kg | 12/16/99 | 300.5 Kg | 60665CB00 | 269.2 Kg (3/3)* |
| Campaign 6 | 2/28/00 | 280 Kg | 2/23/00 | 321 Kg | 62796CB00 | 315.5Kg (3/6)* |
| Campaign 6 (IV) | 2/28/00 | 15 Kg | 2/22/00 | 20 Kg | 62797CB00 | 18 Kg (3/15)* |
| Campaign 7 | 3/30/00 | 300 Kg | 4/10/00 | 370 Kg | 63890CB00 | 361.2 Kg (4/18)* |
| Campaign 7 (IV) | 3/30/00 | 5 Kg | 3/29/00 | 19 Kg | 63889CB00 | 17.2 Kg (4/11)* |
| Campaign 8 | 4/25/00 | 200 Kg | 5/11/00 | 263 Kg | 64970CB00 | 256.5 Kg (5/15) |
| Campaign 8 (IV) | 4/25/00 | 15 Kg | 4/25/00 | 19.8Kg | 64971CB00 | 17.7 Kg (5/11)* |
| Campaign 9 | 6/15/00 | 300 Kg | 6/14/00 | 375.7 Kg | 65064CB00 | 355.7 Kg (6/20/00) |
| Campaign 9 (IV) | 6/15/00 | 15 Kg | 6/5/00 | 18.1Kg | 65065CB00 | 16.7 Kg (6/9/00)* |
| Campaign 10 | 7/15/00 | 300 Kg | 7/26/00 | 361.2 Kg | 67176CB00 | 359.0 Kg (8/10/00) |
| Campaign 11 | 8/15/00 | 300 Kg | 8/4/00 | 333.7 Kg | 68285CB00 | 271.9 Kg (9/7/00) |
| Campaign 12 | 10/6/00 | 300 Kg | 9/27/00 | 356 Kg | 69458CB00 | 292.3 Kg (12/8/00) |
| Campaign 13 | 11/23/00 | 300 Kg | 11/15/00 | 351.2 Kg | 71665CB00 | 349.1 Kg (12/20/00) |
| * Weight after rework | | | Total (year 2000) | 2,815.5 Kg | | |

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Eugene X
Sun/LAKE/PPRD/ABBOTT
02/22/2001 06:57 PM

To Stan Bukofzer/LAKE/Al/ABBOTT@ABBOTT
cc
bcc
Subject 773 material

Stan,
here are some background materials



ABT-773 Development Plan 1.doc



Leiden review Dec00.ppt



End of Phase 2 Meeting Minutes.doc



End of Phase 2 Meeting - Primary Slides.ppt



ABT773 Review Pharma Exe Meeting.rtf



ABT-773 Pharma Exe Meeting.ppt

ABT-773 DEVELOPMENT PLAN

C. Meyer [DATE]

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A. Executive Summary

A.1 SWOT Analysis

| Table A.1 SWOT Analysis (Strengths/Weaknesses/Opportunities/Threats) | | |
|----------------------------------------------------------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| CATEGORY | ITEM (Probability/Impact) | STRATEGY |
| Strengths | <p>ABT-773 is active against penicillin-resistant and macrolide-resistant <i>S. pneumoniae</i> including Firm AM and Mef phenotypes; it has not been shown to induce M^rS₆ (macrolides, lincosamides and streptogramin B) resistance.</p> <p>The in vitro microbiological profile of ABT-773 shows a 4-fold superiority to telithromycin which should translate into 3 to 5 times lower daily dose than the first ketolide.</p> | <p>Key positioning in the marketplace as a safe, effective antibiotic that treats resistant organisms and does not induce resistance.</p> <p>Capitalize on micro superiority and lower dose by generating comparative efficacy/safety data in Phase IIIb studies.</p> |
| Weaknesses | <p>Pharmacokinetic profile does not meet the preconceived ideas of some PK/PD experts. Because of this, the 150mg QD dose may be challenged.</p> <p>In Phase IIb studies, 300 mg QD has higher GI/taste perversion adverse events compared to clari 500 mg BID</p> <p>The Phase III clinical program is large, intense, and must be conducted successfully in a relatively short period of time. There is also very stiff competition from other major pharmaceutical companies to enroll patients. Many of these companies are paying inflated grants fees and have simpler Phase IV protocols that will entice investigators.</p> <p>An IV and pediatric formulation will not be available at launch. An IV formulation would further enable us to position this product as an effective drug for a range of mild to severe infections. A pediatric formulation would further underscore the safety properties of the product. Both formulations would promote improved acceptance of this product.</p> | <p>Phase IIb studies indicated efficacy with 150 mg daily dose in ABECB and ABS. PK/PD data together with ribosome kinetics support the decision to proceed with 150mg QD in mild infections (ABECB and ASP) and select between 150mg BID and 150mg QD in CAP and ABS. Recent PK/PD data support AUC of 1-6 for clinical exposure in CAP necessary for cure.</p> <p>Monitor enrollment closely and be proactive with CROs in opening additional sites and offering appropriate incentives to push enrollment. Prepare to open sites in the Southern hemisphere.</p> <p>HPD has identified initial funding this year to bring an IV prototype into Phase I studies. Further development funding has been requested in 2001 in the IIPD plan and has been included in a PPD blue plan request.</p> <p>Present initial pediatric Phase I data as well as taste evaluation will be available mid-October for management decision on future funding.</p> |
| Opportunities | <p>ABT-773 has the potential to be able to address competition with azithromycin with short course therapy for mild infections, as well as quinolones for more serious infections. Resistance (PRSP/MRSP) is a growing concern and will be a major consideration when this product is introduced.</p> | <p>Conduct appropriate comparative Phase III studies to get approval for all the RTI indications, both in U.S. and European countries. Collect enough resistant isolates to obtain the claim for resistant <i>S. pneumoniae</i>.</p> |

| | | |
|----------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| | <p>If 150mg QD is proven effective, COGs for this product will be within a very acceptable range for obtaining a high profit margin in all markets.</p> <p>Obtain sufficient quantity of clinical isolates with resistant organisms to request a separate claim for activity against resistant <i>S. pneumoniae</i>.</p> | <p>Continue to improve throughput and yield and introduce appropriate process improvements in SPD to further bring down the bulk drug costs. Propose intermediate step 5 as the starting material for the bulk drug to enable further process improvements post-filing.</p> <p>This opportunity exists for the FDA labeling only and recent information indicates that FDA is rethinking their position on granting this separate claim. Other antibiotics have been granted this claim with as little as 15 isolates.</p> |
| Threats | <p>Current data available is insufficient to predict that 150mg QD will be effective in more serious indications of CAP and Sinusitis. Current two dose studies are being carried out in 150mg QD and 150mg BID to assess the potential of 150mg BID being the required dose for these indications.</p> <p>Regulatory uncertainties over how to deal with ketolide/macrolide class</p> <p>Elevated liver enzymes were seen in a small number of Japanese volunteers in a PK study.</p> <p>The Japanese development program has been delayed due to findings in the first Japanese PK study indicating a significant difference in the PK profiles between Japanese and non-Japanese subjects. Timing, dose selection and funding for the Japanese program is unknown at this time.</p> | <p>May need to market 150mg QD for mild infections and 150mg BID for more severe infections.</p> <p>ABT-773 is similar to clarithromycin and erythromycin in its effect on QT intervals in preclinical studies. Current clinical data indicates no evidence of QTc prolongation. ECG monitoring is included in all the Phase III studies. An HPD funded phase I study of an IV formulation prototype will provide additional information on QTc prolongation.</p> <p>Current expert analysis has concluded that there no clinically significant interaction. The study is being repeated in Japan to further evaluate.</p> <p>Repeat Japanese PK study in Japan along with a food effect study. Once results are available, meet with clinical advisory committee KIKO and determine the development requirements for Japan.</p> |

A.2 Development Plan Summary

Considering the rapid and extensive emergence of penicillin and macrolide resistant *S. pneumoniae*, and the remaining patent life of Clarithromycin, the flagship of Abbott's pharmaceutical product line, ABT-773 was approved by PPCC in 03/97 as a candidate for Development by the Anti-Infective Venture. The mission of the Venture is to develop ABT-773

as a first line therapy in community acquired lower and upper respiratory infections (RTIs).

The proposed indications and treatment durations below position this product to compete effectively in the RTI arena both in the U.S. and in international markets. These are the required indications to be considered as first line therapy for RTIs.

- | | |
|------------------------------------------------------|---------|
| • Community-Acquired Pneumonia | 10 Days |
| • Acute Bacterial Sinusitis | 10 Days |
| • Acute Bacterial Exacerbation of Chronic Bronchitis | 5 Days |
| • Acute Streptococcal Pharyngitis/Tonsillitis | 5 Days |

Our goal is to provide the physician with an agent which will have the safety and tolerability of azithromycin for mild to moderate infections but with the strengths of the quinolones for moderate to severe infection of the respiratory tract particularly for (PRSP/MSRP) resistant *S. pneumoniae*.

We will also be seeking additional labeling to include the treatment of macrolide-resistant *Streptococcus pneumoniae*, penicillin-resistant *Streptococcus pneumoniae*, and atypical pathogens to include *C. pneumoniae*, *M. pneumoniae* and *L. pneumophila* in the above-mentioned indications. Susceptibility and clinical treatment trial data for macrolide-resistant *Streptococcus pneumoniae* and penicillin-resistant *Streptococcus pneumoniae* will be provided from Phase 3 trials. A request for appropriate breakpoints to include these strains will also be provided in the NDA.

B. Marketplace

B.1 Marketplace SWOT Analysis

| Table B.1a SWOT Analysis (Strengths/Weaknesses/Opportunities/Threats) | | |
|-----------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------|
| CATEGORY | ITEM (Probability/Impact) | STRATEGY |
| Strengths | Large market in terms of both prescriptions and sales | None |
| | Emerging international markets may contribute to positive market growth ex-U.S. | Move forward with global development program |
| | Antibiotic resistance ultimately renders older agents obsolete, allowing newer agents access to the market | Target resistance claim for ABT-773 |
| | | |
| Weaknesses | May be negative pressure on antibiotic usage stemming from increasing antibiotic resistance | Monitor appropriate use guidelines and their impact on antibiotic usage; where possible, attempt to influence decision making bodies (FDA, CDC, NCCLS) |
| | Difficult to differentiate antibiotics | Leverage product strengths (targeted RTI spectrum, activity, ribosome binding) to create a differentiation strategy |
| | High hurdle rate for new agents in terms of convenience and adverse event profile | Evaluate ABT-773 profile upon receipt of phase III data |
| | High level of promotional support required to reach optimal sales levels | Build adequate promo levels into LRP |
| Opportunities | ABT-773 represents a hedge against Biaxin IR patent expiration in 2005 | Evaluate optimal portfolio/promo strategy between Biaxin XL and 773 in light of patent expiration |
| | Potential for I.V. formulation, expands scope of franchise into new market segment | Continued funding of IV program |
| | Potential for pediatric formulation | Make go/no go decision based on taste/17K data |
| | | |
| Threats | Telithromycin launch 2-1/2 years in advance of ABT-773 | Monitor launch of telithromycin, adjust 773 strategy if necessary based on market feedback |
| | Considerable number of antibiotics lose patent exclusivity by 2005-may put negative price pressure on market | Work with managed care group to evaluate potential impact |
| | May be negative pressure on antibiotic usage stemming from increasing antibiotic resistance | Monitor appropriate use guidelines and their impact on antibiotic usage; where possible, attempt to influence decision making bodies (FDA, CDC, NCCLS) |
| | New entrants | Leverage product strengths (targeted RTI spectrum, activity, ribosome binding) to create a differentiation strategy |

B.2 Epidemiology/Disease Class

Respiratory tract infections represent the majority of community-acquired infections. Causative pathogens for these infections are most often *Srep. pneumoniae*, *H. influenzae*, *M. catarrhalis*, and *M. pneumoniae*. Table X summarizes the annual incidence of community-acquired respiratory infections.

Table B.2.1: Annual Incidence of Community-Acquired Infections

| | Infection | Annual Incidence (U.S., millions) | Annual Incidence (Ex-U.S., millions) |
|-------------------|-------------|--------------------------------------|-----------------------------------------|
| Upper Respiratory | Sinusitis | 37 | 94 |
| | Otitis | 18 | 46 |
| | Pharyngitis | 12 | 30 |
| Lower Respiratory | Bronchitis | 14 | 36 |
| | Pneumonia | 4 | 10 |

B.3 Market Overview

U.S. Market

1999 U.S. antibiotic prescription and sales data are presented in the table below.

| | | | 1995 | 1996 | 1997 | 1998 | 1999 | CAGR ₉₅₋₉₉ |
|------|-----------------|------------|---------|---------|---------|---------|---------|-----------------------|
| U.S. | INXs (MM) | Tab/Cap | 220 | 215 | 211 | 208 | 221 | 0.1% |
| | | Oral Susp. | 76 | 66 | 63 | 59 | 61 | -5.3% |
| | | I.V. | NA | NA | NA | NA | NA | NA |
| | Sales (\$MM) | Tab/Cap | \$4,057 | \$4,220 | \$4,467 | \$4,848 | \$5,715 | 8.9% |
| | | Oral Susp. | \$1,075 | \$979 | \$977 | \$1,001 | \$1,120 | 1.0% |
| | | I.V. | \$1,865 | \$1,829 | \$1,855 | \$1,890 | \$2,117 | 3.2% |

Tab/cap and oral suspension prescriptions had been declining 1-2% per year in the period of 1995-1998, presumably from increased attention to appropriate prescribing in the face of increasing resistance; however, prescriptions recovered in 1999, though this may be explained at least in part by a relatively late 1998-99 flu season. Even in the face of this negative pressure on antibiotic use, however, sales in the U.S. have continued to increase, particularly in the tab/cap market. This is due to the trend of replacing relatively low-cost generic agents with higher priced premium antibiotics; during 1995-1999, generic tab/cap prescriptions declined by 30MM. So while negative pressure on the use of these antibiotics continues, it appears the market is willing to bear higher costs for agents that meet unmet need. The I.V. market has grown slightly in terms of sales, also being driven largely by the replacement of generic agents with more costly branded agents.

The macrolide class has grown significantly over recent years, from \$771MM in 1995 to \$1,596MM in 1999, though most of this growth (\$673MM) was due to gains in Zithromax, underscoring the importance of convenience, adverse event profile, and price in this market.

Ex-US Market

The ex-US antibiotic market had sales of \$11.6B in 1999, an increase of approximately 5.9% over 1998; however the CAGR over the past 3 years has been only 0.7%. Antibiotic usage is expected to decline 1-2% per year in the largest, most developed AI regions – Europe, Japan and Canada; however, Latin America and PAA are expected to show 1.5% - 3.0% growth as access to healthcare continues to improve. Standard units (used as a proxy to normalize units across regions) have decreased approximately 1.7% versus prior year, despite strong sales growth. This reflects a gradual shift to newer, premium priced agents, particularly in less developed regions.

Clarithromycin performance in AI markets continues to be strong, out-performing azithromycin sales and growth rate by almost 3 to 1. Although the ex-US quinolone class market share (15.3%) significantly lags US performance (28.4%), the quinolones show strong growth, fueled in part by new product introductions such as levofloxacin. It should be noted, however that almost 80% of Levo sales are in Japan, where sales increased 40% over the previous year. Levo launched in 1994 in Japan, but has only recently been introduced in other ex-US markets. Moxifloxacin was launched Q4 1999 in Germany, and has begun roll-out to other European markets in 2000. Moxi has not yet been submitted in Japan. Gatifloxacin approval is expected for European markets in Q2 2001, and is currently in Ph III for Japan. Cephalosporins continue to dominate the ex-US market, with sales share of over 40% (compared to only 17% in the US).

Table B 3.b Ex-US Sales

| | 1999 Sales | | | 1999 Standard units | | |
|------------------------------|-----------------|--------------|----------------|---------------------|-------------|----------------|
| | Sales (\$000s) | Share | Growth (99/98) | SU (000s) | Share | Growth (99/98) |
| Penicillins | \$2,475 | 21.2% | 0.8% | NA | NA | NA |
| Augmentin | \$684 | 5.9% | 1.9% | 1,213 | 6.4% | 2.0% |
| Amoxicillin | \$684 | 5.9% | -8.1% | 3,479 | 18.3% | -1.9% |
| Cephalosporins | \$4,948 | 42.3% | 7.5% | NA | NA | NA |
| Cefaclor (Ceclor) | \$344 | 2.9% | -8.0% | 638 | 3.4% | -8.9% |
| Cef. Axetil (Ceflin) | \$288 | 2.5% | 2.9% | 261 | 1.4% | 2.7% |
| Cef. Proxetil (Vantin) | \$185 | 1.6% | 7.0% | 186 | 1.0% | 3.9% |
| Ext. Spec. Macrolides | \$2,257 | 19.3% | 5.1% | NA | NA | NA |
| Clarithromycin | \$904 | 7.7% | 12.0% | 816 | 4.3% | 8.3% |
| Azithromycin | \$344 | 2.9% | 4.1% | 113 | 0.6% | 4.6% |
| Roxithromycin | \$253 | 2.2% | 0.1% | 257 | 1.4% | -0.8% |
| Quinolones | \$1,788 | 15.3% | 11.1% | NA | NA | NA |
| Ciprofloxacin | \$530 | 4.5% | 1.2% | 404 | 2.1% | 4.7% |
| Levofloxacin | \$467 | 4.0% | 54.0% | 248 | 1.3% | 31.2% |
| TOTAL | \$11,685 | 100% | 5.9% | 19,031 | 100% | -1.7% |

Source: IMS retail pharmacy data for all formulations, all audited ex-US markets; standard units used as a proxy for prescription market share, since Rx's are not audited in most ex-US markets

B.4 Current Treatment Options

| Class | Mechanism of Action | Comments |
|----------------|-------------------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Penicillins | Cell wall synthesis inhibitor | Mostly generic, class has seen significant decrease as a result of penicillin resistance |
| Cephalosporins | Cell wall synthesis inhibitor | Some generic, class has seen significant decrease in use as a result of prevalence of B-lactamase producing strains |
| Tetracyclines | Protein synthesis inhibitor | Generic agents, relatively high levels of resistance but are still useful in some indications |
| Sulfonamides | Folic acid synthesis | Generic agents, relatively high levels of resistance but are still useful in some indications |
| Macrolides | Protein synthesis inhibitor | Widespread use in RTI, macrolide resistance has been increasing rapidly, but has not yet translated into declines in clinical efficacy; IL flu activity continues to be class weakness, along with GI events, drug-drug interactions, & taste perversion |
| Quinolones | DNA synthesis inhibitor | Fastest growing antibiotic class, used in broad spectrum of indications; class historically associated with poor Gram+ pathogen coverage and sub-optimal safety profiles; newer agents (Levaquin, Tequin, Avelox) have improved dramatically along both spectrum and safety dimensions. |
| Oxazolidinones | Protein synthesis inhibitor | Newest antibiotic class to reach market, due to limited Gram profile and potential safety issues will be used primarily in nosocomial setting |

B.5 Competitive Analysis – Emerging Competition

| <i>Table B.5a Pipeline</i> | | | | | |
|----------------------------|-----------------|------------------------|---------------------------------------|--------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| <i>Product</i> | <i>Company</i> | <i>Class</i> | <i>Phase/Estimated Time to Market</i> | <i>Country</i> | <i>Comment</i> |
| Ketek (telithromycin) | Aventis | Ketolide | Filed 3/00 Est. launch 3/01 | U.S. | Respiratory indications; filed NDA 3/00; 800 mg QD; first in ketolide class to reach market. |
| Factive (gemifloxacin) | SKB | Quinolone | Filed 12/99 Est. launch 12/00 | US | Superior to other quinolones for MRSA; highly potent vs. RTI pathogens H. flu, M. cat, and S. pneumo and UTI pathogens E. coli and P. mirabilis, CRSP; potency > spar, trov, grep and ≥ moxi; activity vs. P. aeruginosa; good atypical and mycoplasma coverage; intracellular penetration; low photo/CNS tox; 700 patient database |
| Stadoloxacin | Daiichi Seiyaku | Quinolone (IV only) | III II Est. launch 2002 | Japan U.S., Europe | Potent against MRSA, pseudomonas and bacteroides activity; diarrhea, ALT, low WBC; phototox issues; will likely target severe rather than community infections |
| Ecenofloxacin | Chiesi Foods | Quinolone | II Est. launch 2002 | UK | Active against UTI and RTI pathogens; superior to lome and oflo vs. P. aeruginosa. T _{1/2} = 14-19 hr; will likely be target to severe rather than community infections |
| CS-940 | Sankyo | Quinolone | II Est. launch 2002 | Japan | Active against G+/G-; excellent activity against H. flu, c. jejuni, M. pneumo, and C. trachomatis; greater potency than cipro; t _{1/2} < 7 hr; BA ~80% |
| T-3811 | Toyama/BMS | Quinolone | I Est. launch 2005 | Japan | Excellent potency and low toxicity |
| ABT-492 | Abbott | Quinolone | Pre-clin Est. launch 2005 | US | Excellent potency, good anti-pseudomonal activity. To initiate phase I 11/00 |
| DC-756 | Daiichi Pharma | Quinolone | Pre-clin Est. launch 2006 | Japan | Low toxicity; in vitro potency ≥ trov, STTX & HSR-903 |

B.6 Unmet Needs

Overall unmet need in the anti-infective market is low. Resistance represents the largest unmet need, which will continue to evolve over time. Satisfaction with other product attributes, such as convenience, spectrum of activity, and tolerability/safety is quite high. Any improvements in these areas will be incremental and will offer little in the way of differentiation. Table B.6a shows the impact of the pipeline on current unmet market needs.

| <i>Table B.6a Unmet Market Needs and the Impact of the Pipeline</i> | |
|---------------------------------------------------------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| <i>Unmet Need</i> | <i>Pipeline Impact</i> |
| Activity against resistant organisms | Strep. pneumo, MRSA, and VRE represent most problematic pathogens although new quinolones/ketolides do well with most resistant Strep. pneumo strains; quinolone-resistant Strep. pneumo may develop; pseudomonas resistance is also increasing; resistance will likely continue to be a source of unmet need due to its dynamic nature. |
| Low propensity for resistance development | Given that most compounds in development are from classes of drugs already in use, this need is largely unmet. Unclear how quickly resistance will build to new classes of drug; gatifloxacin claims 8-methoxy functional group results in lower propensity for resistance development |
| Convenience (duration/frequency) | Standard moves toward 5-7 days of therapy with QD dosing; may start to see 3-day therapies for some indications (AECB) |
| Increased tolerability | While some degree of unmet need exists, increasingly, agents (which have not been withdrawn) are reaching the marketplace with adverse event profiles that approach clinical insignificance; a very clean safety profile should be regarded as a necessary component rather than a differentiating one |
| Few drug-drug interactions | Quinolones, macrolides, and ketolides all interact with other drugs to varying degrees; a potent drug with no interactions would be a benefit in this market |

C. Product Positioning

C.1 Product Positioning Options

| Positioning Alternative | Strategy | Strengths | Weaknesses |
|---------------------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Macrolide replacement | Convert existing macrolide business (including Biaxin) to ABT-773. Desirable if Biaxin XL erosion is expected to be high upon launch of IR generics | Relatively simple strategy to implement & communicate to market Large Zithromax business to target Strategy is a natural extension of 773's activity against macrolide-resistant <i>S. pneumoniae</i> | Sales are at expense of Biaxin Will need to achieve a very good tolerability & convenience profile to maximize this strategy May be difficult to keep business from shifting toward generic clarithromycin |
| Second line (macrolide-sparing) | Co-position Biaxin and ABT-773. Desirable if Biaxin XL erosion is expected to be low upon launch of IR generics | Sales of 773 would be at least partially additive to Biaxin Support of both Biaxin and 773 may allow a broader scope of the RTI market to be served Allows for greater flexibility with price, potential for advantageous price/volume scenarios | Can be difficult to segment & communicate to reps/physicians |
| Quinolone fighter | Position as a potent alternative to quinolones for RTIs | RTI-specific spectrum of 773 could play well if quinolone resistance develops RTI-specific spectrum of 773 is consistent with "appropriate use" Quinolones are fast-growing market segment | May be difficult to convince physicians that 773 is as potent II. flu activity of 773 is inferior to quinolones |

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C.2 Target Product Profile

C.2.1 ABT-773 Target Product Profile

Table C.2.1 outlines the desired target product profile for ABT-773

| Product Profile | | | | |
|-------------------------------------------------------------------------------------------------|--------------|--------------|----------------|--------------|
| Attribute | Date Defined | Probability* | Confirm Status | Share Impact |
| Activity against Gram +, Gram -, atypicals | 3/1997 | High | Confirmed | High |
| Activity against <i>H. influenzae</i> = azi | 3/1997 | High | Confirmed | High |
| Active against 80% of Gram + resistant strains of efflux and MLS-c | 3/1997 | High | Confirmed | High |
| Active against most macrolide resistant pathogens on a bacterial-worldwide-susceptibility panel | 3/1997 | High | Confirmed | High |
| Incidence of GI side effects=azi | 3/1997 | Low | Not Met | High |
| Incidence of drug-interactions = clari, no contraindications | 3/1997 | High | 6/2001 | Medium |
| QD dosing adult/tablet | 3/1997 | Medium | 6/2001 | High |
| QD dosing ped OS | 3/1997 | Medium | 9/2000 | Medium |
| QD dosing for IV | 3/1997 | Medium | 12/2000 | High |
| Comparable pain at injection site than azi | | Medium | 12/2000 | Low |
| Less metallic taste than clari XL | 3/1997 | Medium | 6/2001 | High |
| OS equal in taste to Azi, Omnicel | | Low | 9/2000 | High |
| 5-day therapy for most indications | 3/1997 | Low | 6/2000 | High |
| COGS > 80% SMM at launch | 3/1997 | High | 12/2001 | Low |
| Maintain balanced plasma/tissue levels similar to clari | | Medium | 12/2001 | Medium |

* Probability Key:
 High = 70-100%
 Medium = 50-69%
 Low = 0-29%

Table C.2.2 outlines the product profile strengths, weaknesses, opportunities and threats.

| Table C.2.2 SWOT Analysis (Strengths/Weaknesses/Opportunities/Threats) | | |
|------------------------------------------------------------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| CATEGORY | ITEM (Probability/Impact) | STRATEGY |
| Strengths | Macrolides/ketolides are regarded as an "appropriate" choice for RTIs; could be used to advantage should quinolone resistance develop | Leverage recent guidelines to develop support for class in RTIs; monitor quinolone resistance surveillance |
| | ABT-773 is generally regarded as more potent than telithromycin and macrolides against Gram-positive causative RTI pathogens, including resistant pathogens ABT-773 may offer unique mechanistic advantages relative to telithromycin and macrolides (ribosome binding) | Utilize in vitro and animal model data to build conceptual argument for 773 relative to telithromycin and other agents via advisory panels, symposia, etc. Utilize in vitro and animal model data to build conceptual argument for 773 relative to telithromycin via advisory panels, symposia, etc. |
| Weaknesses | Potential for perceived weakness of product with respect to PK profile at 150 mg dose | Identify strategy to "explain" clinical data in light of PK issue; "ribosome story" |
| | H. flu microbiological activity inferior to quinolones Phase II data suggests moderate levels of diarrhea and taste perversion | May be able to mitigate if clinical eradication data is strong; re-evaluate after receipt of phase III data Telithromycin appears to have even higher diarrhea rate; consider phase IIIb/IV comparative study |
| Opportunities | Potential for I.V. formulation, has positive impact on image of tablet | Continued funding of IV program |
| | Potential for pediatric formulation, has positive impact on image of tablet | Make go/no-go decision based on taste/PK data |
| Threats | May be BID dosing for CAP and/or sinusitis-all recent antibiotics have QD dosing for all indications | Proceed with dose ranging phase III to determine if QD dosing is adequate for these indications |
| | H. flu eradication may be sub standard at 150 mg dose Telithromycin may gain 5-day indication for sinusitis-no other antibiotics have 5-day claim Requisite number of resistant isolates for claim may not be achievable for NDA; may require additional trials | Evaluate in light of phase IIIa data (2Q01) In light of phase IIIa data, evaluate whether 5-d vs 10-d ABT-773 arm could be added to gain 5-day indication Evaluate situation at completion of phase III clinical program |

C.2.2 Target Product Label - See Appendix 1

C.3 Reimbursement/Pricing Strategies

C.3.1 Reimbursement/Managed Care

Development of reimbursement strategies will be initiated upon completion of the phase IIIa studies, at which time product dosing will have been determined and more certainty to efficacy/AE rates will have been obtained.

C.3.2 Pricing Strategy

- a) U.S pricing for 5 days of ABT-773 will be at parity with 5 days of Zithromax, allowing ABT-773 to effectively compete for Zithromax business.
- b) Pricing in most European markets will be set by the government, and will be somewhat dependent on how the ketolide is classified – as a macrolide or as a new class that merits a price premium vs. the macrolide class. Although a price premium would increase revenue per unit, it could potentially limit market penetration, and therefore, reduce total revenue opportunity. Clari will be subject to downward pricing pressure due to European and Japanese price control measures and to generic incursion in LA and PAA markets over the next few years. Therefore, the base case pricing assumption is that ABT-773 will achieve pricing comparable to current clari price per course of therapy.

C.4 Sales Forecast(s) for ABT-773**C.4.1 U.S. Sales Forecast**

The U.S. forecast is shown in Table C.4.1a, below:

| Table C.4.1a U.S. Forecast (Date of Forecast: 7/00) | | | | | |
|------------------------------------------------------------|-------------|-------------|-------------|-------------|-------------|
| | 2004 | 2005 | 2006 | 2007 | 2008 |
| Market (MM TRX)* | 195 | 193 | 191 | 189 | 187 |
| - % chg | -1.0% | -1.0% | -1.0% | -1.0% | -1.0% |
| Abbott Share (%) | 2.1% | 3.2% | 4.2% | 5.3% | 6.2% |
| Abbott TRX (MM) | 4.1 | 6.2 | 8.1 | 10.0 | 11.7 |
| Price/Rx (\$, avg) | \$35 | \$34 | \$32 | \$33 | \$34 |
| Abbott Sales (\$MM) | \$139 | \$199 | \$265 | \$335 | \$399 |
| R&D (\$MM) | \$30 | \$30 | \$30 | \$30 | \$20 |
| SG&A (\$MM) | \$101 | \$83 | \$86 | \$99 | \$115 |
| SMM (%) | 88% | 90% | 90% | 90% | 91% |
| Div. Margin (\$MM) | (\$23) | \$44 | \$95 | \$138 | \$174 |

10 year pre-tax NPV @ 12.5% = \$345MM 10 year pre-tax ENVY @ 12.5% = TBD

10 year post-tax NPV @ 12.5% = \$201MM 10 year post-tax ENVY @ 12.5% = TBD

Key Assumptions:

- U.S. approval August 2003
- Market is declining 1% per year on TRX basis
- 150 mg QD dosing for all indications
- 5 day AFEB & pharyngitis; 10 day CAP & sinusitis
- 5 day pack priced at parity to Zithromax; average price per RX shown is after discounts/rebates
- 800M details/year (62% primary, 38% secondary)
- Sampling at parity to current Biaxin levels on basis of courses of therapy sampled
- Peak market share = 6.9% (2009)
- U.S. R&D costs at 60% of total
- NPV does not account for potential cannibalization of Biaxin by ABT-773

Forecast Update Plan:

Forecast will be updated if necessary upon receipt of the phase IIIa data 2Q01.

C.4.2 Ex-U.S. Sales Forecast The ex-U.S. sales forecast is shown in Table C.4.2a, below.

| Table C.4.2a Ex-U.S. Forecast (Date of Forecast: 8/00) | | | | | |
|--------------------------------------------------------|------|------|------|------|------|
| | 2004 | 2005 | 2006 | 2007 | 2008 |
| Market (MM packs)* | 592 | 592 | 593 | 594 | 595 |
| - % chg | 0.0% | 0.0% | 0.1% | 0.2% | 0.2% |
| Abbott Share (%) | 1.1% | 2.3% | 3.3% | 4.3% | 4.9% |
| Abbott packs (MM) | 6.5 | 13.6 | 19.7 | 25.3 | 29.3 |
| Price/Rx (\$) | 12.6 | 12.6 | 12.6 | 12.6 | 12.6 |
| Abbott Sales (\$MM) | 82 | 172 | 248 | 321 | 373 |
| R&D (\$MM) | 4 | 2 | 2 | 2 | 2 |
| SG&A (\$MM) | 84 | 84 | 84 | 76 | 76 |
| SMM (%) | 85% | 88% | 89% | 90% | 90% |
| Div. Margin (SMM) | (19) | 63 | 132 | 199 | 254 |

10 year pre-tax NPV @ 12.5% = \$403MM 10 year pre-tax ENPV @ 12.5% = TBD

10 year post-tax NPV @ 12.5% = \$234MM 10 year post-tax ENPV @ 12.5% = TBD

* packs used as a proxy for Rx's (Rx's not audited in most AI markets)

Key assumptions:

- Ex-US launch lags U.S. by 6-18 months due to pricing negotiations and/or special registration requirements in AI markets
 - Europe (average): U.S. launch + 6 months = Q1 2004
 - LA (average): U.S. launch + 6 months (Q1 2004)
 - PAA (average): U.S. launch + 1 yr (Q3 2004)
 - Japan (average) = US launch + 1 yr (Q3 2004)
 - Canada = US launch + 12-18 mos (Q3 2004)
- Market is declining approximately 1-2.5% in Europe, Japan and Canada, but increasing approximately 2-3% in LA and PAA
- ABT-773 Pack Price = current Clari price per course of therapy
 - Europe: \$10.8./pack (150mg, 5 day); \$22.6/pack (300mg, 7day avg)
 - LA/Canada: \$13.4/pack (150mg, 5day); \$28.2/pack(300mg, 7 day avg)
 - PAA: \$9.7/pack; \$20.4/pack
 - Japan; \$12.8/pack; \$26.8/pack
- Peak Market share (2008): Europe = 6.0%; LA/Canada = 4.6%; PAA = 3.3%; Japan = 5.9%; 90% of pack share from 150mg QD dose strength
- Dosing = 150mg QD 5 day for bronchitis and pharyngitis; 300mg QD 10 day for CAP and sinusitis
- No resistance claim, however, language in label describing in vitro activity against resistant organisms

Forecast Update Plan:

Forecast will be updated by 12/00 after 2001 LRP forecasting cycle, incorporating input from AI affiliates.

C.5 Facilitating Launch and Market Penetration

There are three components of the strategy to facilitate the launch of ABT-773. These are 1) promotional claims 2) communication strategy 3) opinion leader development. These activities are summarized in thesections below.

C.5.1 Desired Promotional Claims

| Desired key message | Regulatory requirement | Measure | Timing | Study Number | Type of message | Probability | Share Impact | Comments/Risk |
|------------------------------------------------------------|------------------------------------------|--------------------------------------------------------------------------------|-------------|-------------------|-----------------------------|-------------|--------------|---------------|
| Low potential for resistance development | TBD | Mutation frequency, sub-MIC serial passages, mutation prevention concentration | In progress | Multiple | In-vitro (implied efficacy) | Medium | Med | |
| Does not induce macrobide resistance | TBD | Ribosome kinetics, MIC evaluations | In progress | Multiple | In-vitro (implied efficacy) | Medium | Med | |
| Claim against penicillin/mac resistant S. pneumo | ~ 15 resistant isolates, high erad. rate | Patient isolates, erad rate (CAP) | 5/2002 | Phase III studies | Efficacy | Low | Med | |
| Lower resource utilization vs comparators | 2 clinical studies | Overall disease cost | 5/2002 | Phase III studies | Economic | Low | Med | |
| Comparable cure/eradication rates to phase III comparators | Clinical studies | cure/erad rate | 5/2002 | Phase III studies | Efficacy | Medium | High | |
| Comparable safety/AE profile to phase III comparators | Clinical studies | safety/AE rate and severity; dropout rate | 5/2002 | Phase III studies | Efficacy | Medium | High | |

C.5.2 Communication Strategy

Following is a summary of the activities to date relating to communication strategy:

- 83 posters have been presented at 8 scientific conferences between 1998-2000
- 8 journal articles have been published in two journals, all published in 2000
- Approximately 72 research studies have been completed, many with the intent to publish
- Approximately 87 research studies are in progress, many with the intent to publish
- Approximately 120 external investigators have completed or are in progress with research studies, many with the intent to publish

Much of the above work has dealt with microbiological and/or animal model data. As the compound moves forward, emphasis will shift to the release of more clinically relevant data. Scientific meetings and journals will continue to serve as the primary channels for dissemination of information, though more specialized communication (symposia, advisories, press releases, etc) will start to be used as a more complete understanding of ABT-773 is gained.

An additional focus of study/communication will be towards capitalizing on the unique ribosome binding properties of the product. Information gained from this initiative may be called upon in defense of the selection of the relatively low 150 mg dose. It may also serve as a means of differentiating the product. Various internal and external investigators are working to gain a greater understanding of the underlying science as well as the properties of ABT-773 in this area. Early in 2001 an internal/external "working group" will be convened to develop a strategy for further study in this area and for the optimal dissemination of this data.

Management of all aspects of the ABT-773 communication plan will be facilitated via an intranet tool currently in development by IM&T and external developers. The completion is targeted for November 2000.

C.5.3 Opinion Leader Development

An ABT-773 advisory board of external opinion leaders has been established and has been convened several times over the last several years. The purpose of these advisories has been to solicit guidance for the development of ABT-773 as well as to positively influence their perception of the ketolide class and ABT-773 in particular. An additional mechanism for opinion leader development has been their involvement in both clinical and non-clinical studies. Approximately 120 external investigators, many regarded as top-tier opinion leaders, have experience with ABT-773. A major initiative as ABT-773 moves forward is to identify key national opinion leaders who have favorable experience/opinion of ABT-773 and to work with them to develop an advocacy strategy for publications, scientific meetings, symposia, and advisories.

D. Regulatory Strategy

D.1 Regulatory Strategy SWOT Analysis

| Table D.1 SWOT Analysis (Strengths/Weaknesses/Opportunities/Threats) | | |
|----------------------------------------------------------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| CATEGORY | ITEM (Probability/Impact) | STRATEGY |
| Strengths | <ul style="list-style-type: none"> QD dosing may be viewed as positive for patient compliance if data is strong | Make sure PK/PD data is available to support dose selection rationale |
| | <ul style="list-style-type: none"> If the drug has a favorable risk benefit ratio with added value compared to existing therapies then the likelihood of approvability is high in EU countries or other countries requiring a CPMP package ABT-773 may present a key point of differentiation with promising activity against macrolide and penicillin resistant <i>Streptococcus pneumoniae</i> and enhanced antibacterial activity <i>in vitro</i>. If proven <i>in vivo</i>, this may indicate favourable relative therapeutic value required for approval and inclusion within local use guidelines. <p>For COF's countries, if the US or EU receives approval then approvals in these LA/PAA countries are assured assuming appropriate sourcing.</p> | <p>The development programs must be designed to unequivocally demonstrate the existence of an added value (e.g. safety or clinical efficacy against resistance species)</p> <p>To utilize the enhanced bacterial activity as a key point of differentiation need to:</p> <ul style="list-style-type: none"> •Ensure clinical program is designed to optimize chances of obtaining desired isolates •Ensure appropriate pk/pd studies are performed •Seek agreement from FDA regarding burden of proof for labeled indication against resistant pathogens |
| Weaknesses | <ul style="list-style-type: none"> Take with food labeling is required to reduce AE's | FDA will still require pivotal bioavailability studies to be done in fasted state. |
| | <ul style="list-style-type: none"> If BID is chosen for either CAP or ABS, diurnal variation may become an issue during FDA review Conformance to Abbotts' & FDA's Electronic Document Management System requirements may impact filing date High COG's for bulk drug driving vendor matrix and push to redefine starting material <p>Harmonization of global clinical trial designs and</p> | <p>Justification must be provided</p> <p>Electronic filing likely to be valued very highly by FDA, so need to manage internal process to see that we can meet requirements</p> <p>Need FDA buy-in from End-of-Phase 2 CMC meeting on starting material and vendor matrix, including stability requirements</p> <p>Communicate with team, international affiliates, international experts and</p> |

| | | |
|----------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| | <p>guidelines</p> <ul style="list-style-type: none"> Differences in medical practice exist worldwide for antibiotics and associated infections Differences in comparator and dosing regimens Stringent EU regulatory environment with antibiotics <p>EU filing will require a harmonized labeling therefore country-specific favourable labeling cannot be pursued (as done with clarithromycin)</p> <p>Two dose scenario with a lower dose chosen for ABECB, Sinusitis and Pharyngitis with a second dose chosen for CAP may provide limited numbers to assess safety of the higher dose</p> <p>Increased resistance awareness may influence stricter requirements and trend away from lowest effective dose</p> | <p>discuss with EU authorities through agency meetings to ensure design of trials and comparators are acceptable</p> <p>Discuss any country specific issues with authorities, international experts and affiliates. Monitor regulatory environment and competitive products.</p> <p>Discuss issue authorities at agency meeting and ensure MAA addresses this issue. May consider Phase IV studies to address this concern.</p> <p>Ensure clinical program includes relative pk/pd studies and can demonstrate clear efficacy at proposed doses. Ensure clinical program is designed to obtain resistance isolates</p> |
| Opportunities | <ul style="list-style-type: none"> Labeling for resistant organisms if isolates are obtained <p>Eligible for Centralised filing process which would provide EU-wide 10 year protection . May also file by Mutual Recognition procedure which more provides flexibility for non-harmonized disease practices (e.g. infectious disease/antibiotics)</p> <p>Once Daily Dosing may enhance compliance</p> | <p>Get agreement with FDA at End of Phase 2 meeting regarding number of isolates required for labeling claim</p> <p>Filing strategy to be determined based on strength of the clinical program and advice received from agencies during planned agency meetings</p> |
| Threats | <ul style="list-style-type: none"> QT prolongation class labeling in Warnings section of labeling Liver enzyme increases in Warnings section of labeling | <p>Get agreement with FDA at End of Phase 2 meeting regarding EKG monitoring in Phase 3 and promote theory that QT prolongation is not class related</p> <p>Ensure that non-clinical and clinical program fulfill the CPMP points to consider on QTc prolongation.</p> <p>Ensure that non-clinical and clinical program addresses potential safety</p> |

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| | | |
|--|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-------------------------------------------------------|
| | <ul style="list-style-type: none"> • Possible failure of short course therapy for Pharyngitis due to more stringent Test of Cure requirement from FDA • If gastrointestinal AT's are high, may affect benefit/risk assessment by FDA • Could be affected by CDC push to reduce antibiotic use; reserve use of drugs effective vs resistant organisms until existing therapies have failed | labeling issues and MAA/NDA addresses these concerns. |
|--|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-------------------------------------------------------|

Registration Strategy and Timelines for Filing

| Table D.2 Registration Strategy and Timelines for Submission | | |
|-------------------------------------------------------------------------------------------------------------------------------------------------------------|--------------------------------------------------------|-------------------------------------------------------------------------------------------------------------|
| REGION | Proposed Submission Date | Justification |
| US | August 2002 | Estimated completion of the clinical program and CMC stability data |
| Europe Filing procedure (Centralised or MRP) to be determined based on strength of clinical data and discussion with authorities | August 2002 | Estimated completion of the chemistry/pharmacy and clinical data |
| Japan Plan to bridge to US data assuming pk profile is similar in Japanese subjects and a successful Phase II bridging study is possible in Japan | TBD, after completion of Phase I local study in Japan. | Bridging obviates the need for a lengthy and expensive Japanese Phase III program. Requires Kiko agreement. |

PART 2

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D.3 Data Requirements and Impact on CMC/Non-Clinical/Clinical Program

| Table D.3 Data Requirements and Impact on CMC/Non-Clinical/Clinical Program | | | | |
|------------------------------------------------------------------------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|---------------------------------|-------------------------|--------------------------------|
| COUNTRY | Guideline Requirement | Probability of Achieving | Impact on Filing | Impact on Approvability |
| US | • Draft Anti-Infective Guidances for CAP, ABECB, ABS & Pharyngitis | High | High | High |
| | • Draft Anti-Infective Guidances General Considerations for Clinical Trials | High | High | High |
| | • Anti-Infective Points to Consider document | High | High | High |
| | • ICH Efficacy Guidances – E1 through E12 | High | High | High |
| | • ICH Safety Guidances – S1 through S7 | High | High | High |
| | • ICH Quality Guidances – Q1 through Q7 | High | High | High |
| Europe | All ICH guidelines as above, plus CPMP points to consider on QT prolongation CPMP guideline on the clinical evaluation of antibacterials DRAFT CPMP guideline for pk/pd | High/Moderate | High | High |
| Japan | All ICH guidelines as above plus local guidelines/JP issues. ICH E5 ethnic bridging guideline. | Moderate/Unknown | High | High |

D.4 Table of Proposed Discussions with Health Authorities

| Table D.4 Table of Proposed Discussions with Health Authorities | | |
|------------------------------------------------------------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----------------------------------------------------------------------------------------------------------------|
| COUNTRY | Reason for Discussion | Proposed timing for Discussion |
| US | <ul style="list-style-type: none"> • End of Phase 2 – Clinical • End of Phase 2 – CMC • Pre-NDA – Clinical • Pre-NDA – CMC | 10/20/00 TBD TBD TBD |
| Europe | <ul style="list-style-type: none"> • Individual agency meetings with UK, Germany, France and Spain to discuss Phase III Clinical program trial designs • Pre-filing meetings to be determined based on filing strategy | UK complete – 07/10/00 Germany complete- 07/21/00 France scheduled – 08/30/00 Spain – to be determined |
| Japan | <ul style="list-style-type: none"> • K1KO- discuss bridging strategy to 300 mg EU/US program • K1KO re-discuss dose justification | Complete June 2000 TBD |

E. Development Cost and Sensitivity Analysis

E.1 Strategic Spending Overview

The tables below describe the major milestones for the ABT-773 Tablet program as well as the Phase II/III studies and associated costs.

| Metrics Dates | |
|---------------------------------------|---------|
| Description | Date |
| DDC Meeting | 3/1997 |
| Start of first GLP animal tox study | 6/1997 |
| First dose in human (beg. Phase I) | 12/1997 |
| First dose in patient (beg. Phase II) | 9/1999 |
| First dose in Phase III | 11/2000 |
| Last Patient/Last Visit | 4/2002 |
| NDA Filing | 8/2002 |
| NDA Approval | 8/2003 |
| Europe (EMEA) Filing | 8/2002 |
| Europe (EMEA) Approval | 8/2003 |
| Japan Filing | TBD |
| Japan Approval | TBD |

| Protocol # - Study Name | Start (1 st Pt) | End (Last CRF) | R/OSS \$000 | Total Target Patients | Actual Enrollment |
|---------------------------------------------------|-------------------------------|-------------------|----------------|--------------------------|----------------------|
| M99-048, Phase II Dose Ranging, ABECB | 9/1/99 | 3/31/00 | 3,885 | 300 | 384 |
| M99-053, Phase II Dose Ranging, Sinusitis | 9/1/99 | 4/30/00 | 3,172 | 300 | 292 |
| M99-054, Phase II Dose Ranging CAP | 9/1/99 | 4/30/00 | 4,089 | 300 | 187 |
| M00-219 Phase III CAP, Dose Ranging | 11/7/00 | 4/30/01 | 14,400 | 800 | 0 |
| M00-216 Phase III ABECB vs. Azithromycin US | 11/7/00 | 4/30/01 | 7,381 | 600 | 0 |
| M00-217 Phase III ABECB vs. Levofloxacin EUR | 11/7/00 | 4/30/01 | 4,600 | 500 | 0 |
| M00-225 Phase III Sinusitis Dose Ranging | 11/7/00 | 4/30/01 | 7,200 | 600 | 0 |
| M00-223 Phase III Pharyngitis vs. Penicillin US | 11/7/00 | 4/30/01 | 4,340 | 520 | 0 |
| M00-222 Phase III Pharyngitis vs. Penicillin EUR | 11/7/00 | 4/30/01 | 5,000 | 520 | 0 |
| M00-226 Phase III Sinusitis vs. Augmentin US | 10/1/01 | 4/30/02 | 4,400 | 450 | 0 |
| M00-220 Phase III CAP vs. Amoxicillin EUR | 10/1/01 | 4/30/02 | 5,700 | 500 | 0 |
| M00-221 Phase III CAP vs. Levofloxacin US | 10/1/01 | 4/30/02 | 8,200 | 450 | 0 |
| M00-218 Phase III Sinusitis vs. quinolone TBD EUR | 10/1/01 | 4/30/02 | 5,300 | 500 | 0 |

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E.2 Base Case Scenario**E.2.a Base Case Scenario for Project:**

| | Prior Years | 1999 | 2000 | 2001 | 2002 | |
|-------------------------|----------------|------|------|------|------|-------|
| Base Program | | | | | | |
| CMC | 17.5 | 28.6 | 31.2 | 22.8 | 14.5 | |
| - PAR/IDC | 4.8 | 5.4 | 8.6 | 7.8 | 4.5 | |
| - SPD | 12.7 | 23.2 | 22.6 | 15.0 | 10.0 | |
| Drug Safety | 3.5 | 2.5 | 3.4 | 1.7 | 1.0 | |
| Other: | 7.4 | 7.7 | 5.0 | 4.6 | 4.0 | |
| Total | 28.4 | 38.8 | 39.6 | 29.1 | 19.5 | |
| Clinical Program | | | | | | |
| Registration | 2.5 | 9.5 | 34.5 | 61.9 | 23.3 | |
| Pricing | | | | | | |
| Marketing | | | | | | |
| Other: | | | | | | |
| Total | 30.9 | 48.3 | 74.1 | 91.0 | 42.8 | 287.1 |

E.3 Upside Scenario**Funding Increase**

If funding were to be increased by 25%, how would that increased funding be used?

- 1) Accelerating Program
 - At this point in the program, additional funding will not accelerate the filing any earlier than the August 2002 date. The current program is intense and needs to be accomplished within a short timeframe. Probability of success in the current program is estimated at 50 to 60%.
- 2) Enhancing Program
 - The pediatric and IV formulations are currently not funded and could continue from the earlier work completed in 2000. Approximately \$21MM is required for the IV development and \$39MM for the pediatric development. The IV program would provide support for marketing this antibiotic for serious infections and help the marketing of the tablet, and the pediatric supports the marketing position that this is a safe drug.
- 3) Enhancing Program within Existing Program
 - Additional funding within the current program would allow for additional patient enrollment incentives or an increase in the number of sites participating in the current Phase III program. This would increase the probability of success in achieving the Aug 2002 filing date.

E.4 Downside Scenario**Funding Decrease**

If funding were to be decreased by, how would that decrease be applied?

- 1) Slowing Program
 - A decrease in program spending would delay the filing of ABT-773 significantly, minimum one year, as RTI indications are seasonal, and the majority of patient enrollment comes from the northern hemisphere.
- 2) Trimming Program
 - Eliminating an indication will cause this filing to be unapprovable as the number of required patients on drug and the four indications being are sought are the minimum RTI indications for approval. The program is only funded currently for one formulation.
 - The current program is currently funded at the minimal acceptable level for approvability by both FDA and AI regulatory agencies.
- 3) Increasing Risk
 - Refer to Item 2 above. Current probability of success for the program is 50 to 60%. Any reduction to the program will significantly delay the filing.

F. Pharmacokinetics/Pharmacodynamics/Phase 1

F.1 PK/PD/Phase 1 SWOT Analysis

Strengths, weakness, opportunities and threats regarding the clinical program for ABT-773 are discussed below:

| Table F.1 SWOT Analysis (Strengths/Weaknesses/Opportunities/Threats) | | |
|----------------------------------------------------------------------|-------------------------------------------------------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------------------------------------|
| CATEGORY | ITEM (Probability/Impact) | STRATEGY |
| Strengths | Phase IIb clinicals and PK/PD data support once daily dosing. | Conduct Phase III for ABECB and pharyngitis at 150mgQD. Further examine 150mgQD for AMS & CAP. |
| | Food has no influence on ABT-773 PK. High drug levels in alveolar macrophages. | Tolerability may require administration with food. This may explain efficacy vs. <i>H. flu.</i> |
| Weaknesses | ABT-773 may require a total daily dose of 300mg for severe infections. | Examine 150mg BID for AMS & CAP and conduct tissue level studies. |
| | ABT-773 is metabolized by and inhibits CYP3A: has potential to cause clinically important drug interactions. | Lowest effective dose (150mgQD) may minimize drug interaction potential. |
| | ABT-773 has low & variable oral bioavailability. Absorption "window" makes ER dosage forms not feasible. | Multiple ER dosage forms tried, none provided adequate bioavailability and true extended release <i>in vivo</i> . |
| Opportunities | At 300mgQD, ABT-773 inhibits CYP3A, but inhibition is less than 250mgBID clarithromycin. | May wish to repeat midazolam (CYP3A substrate) interaction study at 150mgQD or BID. |
| Threats | Disappointing ABT-773 tissue levels (especially WBC and ELF). Competition (Ketek TM) reports higher WBC and ELF levels. | Repeat tissue level studies and in the meantime focus on efficacy data. |

F.2 PK/PD (Clinical)

The Phase 1 program consists of pharmacokinetic, special population, interaction and tissue penetration studies as outlined in section F.3. To attempt to design a once daily dosage form with optimal pharmacokinetics, fifteen prototype formulations were developed for the initial investigations of preliminary safety and pharmacokinetics. Three immediate release and twelve extended release formulations were evaluated with immediate release capsule formulation (IR-A) serving as the reference formulation. After a review of the preliminary data of these studies, an immediate release tablet formulation (IR-C) was chosen for further development based on

pharmacokinetics, safety, and ease of manufacture. Studies in special populations, drug-drug interaction assessments and tissue penetration evaluations have been conducted with formulation IR-C.

Table F.2.a lists all the completed, planned and proposed PK/PD clinical trials for ABT-773:

| Table F.2.a: Clinical PK/PD Trials (Phase 1) | | | | | |
|----------------------------------------------|----------------|------------------------------------------------------------------------|----------------------------------|-----------------|-----------------------------------------------------------------------------|
| STUDY | POPULATION | OBJECTIVE/ PURPOSE OF STUDY | # OF PATIENTS | FUNDED? | LIKELIHOOD OF ACHIEVING OBJECTIVE/COMMENTS |
| M99-105 | Healthy Adults | PK of ABT-773 in WBC Relative to Plasma | N = 8 | Study completed | Poor partitioning of ABT-773 into WBC. |
| M99-007 | Healthy Adults | Compare Concentrations of ABT-773 in BAL & AM to Plasma | N = 43 | Study completed | High concentrations of ABT-773 in AM. Relatively low concentrations in ELF. |
| M99-142 | Healthy Adults | Compare Concentrations of ABT-773 in BAL, ELF, AM, CSF & TLT to Plasma | BAL = 50 CSF = 10 TLT = 10 | Ongoing | |

F.3 Phase 1 Overall Summary

Pharmacokinetic and Safety Studies:

In the first Phase 1 study (M97-716), the pharmacokinetics and safety of ABT-773 (IR-A) were assessed following rising single oral doses (100 – 1200 mg). This study was conducted in two parts with Part I consisting of single rising doses under fasting conditions and Part II a food effect assessment at a single dose of 400 mg. The pharmacokinetics of ABT-773 were linear over the 400 mg to 1200 mg dose range. At doses below 400 mg, the pharmacokinetics appeared to be nonlinear, with AUC increasing more than proportionally with dose. More recent data have indicated that safe and effective doses of ABT-773 in patients will likely be below 400 mg/day and that pharmacokinetic nonlinearity will occur at these clinically-relevant doses. The mean half-lives over the 200 – 1200 mg dose range were between 5.3 - 6.7 hours. Administration of ABT-773 under nonfasting conditions had little or no effect on the pharmacokinetics. The most commonly reported adverse events were taste perversion and/or events related to the gastrointestinal system including abdominal pain, nausea, vomiting and diarrhea. Administration of ABT-773 with food decreased or eliminated the gastrointestinal adverse events but did not affect the incidence of taste perversion.

In the second Phase 1 study (M97-796) the pharmacokinetics and safety of ABT-773 (IR-A) were assessed in a multiple rising dose study. Total daily doses ranging from 200 mg to 1000 mg were administered for seven days. Over the multiple dose range of 200 to 500 mg BID and 200 to 300 mg TID, the pharmacokinetics of ABT-773 appeared to deviate from dose proportionality and time-linearity. The AUCs increased more than proportionally with increasing dose, and accumulation from single- to multiple-dose administration was greater than predicted. At steady state, the half-life ranged between 6.0 and 8.8 hours. ABT-773 pharmacokinetics exhibited diurnal variation, with lower C_{max} and AUC values for doses administered in the afternoon or evening than for doses administered in the morning. In groups who were administered total daily doses of ≥ 600 mg of ABT-773, the most frequently reported adverse event was taste perversion.

In the third Phase 1 trial (M98-889) the relative tolerability of two doses of ABT-773, 100 mg TID and 200 mg TID, was compared with that of clarithromycin 500 mg BID in 153 healthy volunteers. There were no significant differences between the incidence of adverse events between the three regimens except for taste perversion which occurred in 8% of subjects receiving ABT-773 100 mg TID, 34.6% of subjects receiving ABT-773 200 mg TID and in 37.2% of subjects receiving clarithromycin.

Three Phase 1 trials were performed to compare steady state pharmacokinetics and safety after five days of treatment with various doses of ABT-773 (IR-A); 100 mg TID vs. 200 mg TID (M99-011), 300 mg once daily vs. 200 mg once daily vs. 100 mg TID (M99-016) and 100 mg BID vs. 200 mg BID (M99-018). Over these dose ranges, the pharmacokinetics of ABT-773 deviated from linearity. As seen previously, the AUCs increased more than proportionally with dose.

Bioavailability Studies:

Two Phase 1 studies (M98-865 and M98-885) were performed to evaluate the pharmacokinetics of 600 mg once daily doses for four extended-release prototypes of ABT-773 (two per study) administered with food for four days in comparison to formulation IR-A. For the four prototypes, plasma concentration profiles were much lower than those produced by the immediate release reference capsule. As a result, none of these prototypes continued in development.

Seven further Phase I trials (studies M99-023, M99-024, M99-025, M99-026, M99-029, M99-035, M99-042) were conducted to evaluate the pharmacokinetics and safety of ten additional ABT-773 prototypes, two immediate release and eight extended release formulations in comparison to the reference formulation (IR-A). All studies had two, three or four period cross-over designs with nonfasting, multiple once daily or BID ABT-773 5-day dosing in healthy volunteers. Pharmacokinetically, none of the extended release prototype formulations had superior bioavailability compared to the immediate release capsule. In addition, an Intelisite® study (M98-992, not included in the data package) investigating the absorption of ABT-773 confirmed that absorption of ABT-773 from the colon is limited. Due to the solubility profile of the drug, the apparent narrow absorption window, and low absorption from the colon, it appears that an extended release formulation is not feasible. Therefore, optimal bioavailability is expected with an immediate-release formulation rather than extended release formulations. Upon review of the preliminary data, the immediate release formulation (IR-C; M99-024) was chosen for further development as it appeared to be the most robust formulation and demonstrated fewer adverse events and drop-outs than IR-B (M99-023).

Additional biopharmaceutics studies will be conducted to characterize the relative bioavailability/bioequivalence and food effect on the final, production-scale tablet formulation proposed for marketing.

Table F.3.a lists all the completed, planned and proposed clinical trials for ABT-773:

| Table F.3.a: Clinical Trials (Phase 1) | | | | | |
|----------------------------------------|----------------|------------------------------------------------------------------------------------------------------|----------------------------|-----------------|------------------------------------------------------------------------------------------------------------------------------------|
| STUDY | POPULATION | OBJECTIVE/PURPOSE OF STUDY | # OF PATIENTS | FUNDED? | LIKELIHOOD OF ACHIEVING OBJECTIVE/COMMENTS |
| M97-716 | Healthy Adults | Rising Single Oral Doses of ABT-773 in Nonfasting and Fasting Subjects | Part 1 = 56 Part 2 = 24 | Study complete | ABT-773 PK were nonlinear. Food has no effect on ABT-773 PK |
| M97-796 | Healthy Adults | Rising Multiple Oral Doses of ABT-773 | N = 83 | Study complete | ABT-773 PK were nonlinear and had diurnal variation. If the final to-be-marketed regimen is QD, FDA may ask an AM vs. PM PK study. |
| M99-992 | Healthy Adults | ABT-773 PK Comparing Oral IR Capsule to Intellisite [®] Capsule (Targeted Release in Colon) | N = 10 | Study completed | ABT-773 is very poorly absorbed from colon. |
| M99-011 | Healthy Males | ABT-773 PK Comparing 100mgBID to 200mgBID | N = 12 | Study completed | ABT-773 AUC increased more than proportionally with dose and had diurnal variation. |
| M99-016 | Healthy Males | ABT-773 PK Comparing 300mgQD & 200mgQD to 100mgTID | N = 24 | Study completed | ABT-773 AUC increased more than proportionally with dose and greater exposure achieved by QD vs. TID dosing. |
| M99-018 | Healthy Males | ABT-773 PK Comparing 100mgBID to 200mgBID | N = 24 | Study completed | ABT-773 AUC increased more than proportionally with dose and had diurnal variation. |
| M99-024 | Healthy Males | ABT-773 PK Comparing 150mg IR-C Tablet to 100mg Capsule | N = 18 | Study completed | Prototype C tablet was bioequivalent to the reference capsule. Greater exposure achieved by QD vs. BID dosing. |

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| Table F.3.a: Clinical Trials (Phase 1) Cont. | | | | | |
|----------------------------------------------|----------------------------------------------|--------------------------------------------------------------------------|------------------|----------------------|-----------------------------------------------------------------------------------------------------------------------------------------|
| STUDY | POPULATION | OBJECTIVE/ PURPOSE OF STUDY | # OF PATIENTS | FUNDED? | LIKELIHOOD OF ACHIEVING OBJECTIVE/COMMENTS |
| Special Population Studies | | | | | |
| TBD | TBD | Effects of Age and Gender on ABT-773 PK | | Protocol TBD | ABT-773 clearance may increase with age. Clarithromycin AUC higher in females than in males. |
| M99-127 | Severe Renal Impaired vs. Healthy | Effects of Renal Impairment on ABT-773 PK | | Protocol in progress | No effect of renal impairment on ABT-773 PK expected. |
| M99-119 | Healthy Adults | ABT-773 Single and Multiple Dose Ranging PK in Japanese vs. Non-Japanese | N = 84 | Study completed | At equal doses, Japanese had about 50% greater plasma ABT-773 concentrations than non-Japanese. Lower dose needed in Japanese patients. |
| M99-126 | Mild & Moderate Hepatic Impaired vs. Healthy | Effects of Hepatic Impairment on ABT-773 PK | N = 24 | Ongoing | |

| Table F.3.a: Clinical Trials (Phase 1) Cont. | | | | | |
|----------------------------------------------|-----------------------|----------------------------------------------------------------------------|---------------|-----------------|-------------------------------------------------------------------------------------------------------------------------------------------|
| STUDY | POPULATION | OBJECTIVE/PURPOSE OF STUDY | # OF PATIENTS | FUNDED? | LIKELIHOOD OF ACHIEVING OBJECTIVE/COMMENTS |
| Drug Interaction Studies | | | | | |
| M99-128 | Healthy Adult Females | Effects of ABT-773 on the PK of OC's | N = 18 | Study completed | No clinically significant drug interaction was observed. |
| M99-138 | Healthy Adults | Effects of Ketoconazole (CYP3A inhibitor) on PK of ABT-773 | N = 18 | Study completed | Ketoconazole inhibited ABT-773 metabolism increasing ABT-773 AUC >5 times. |
| M99-139 | Healthy Adults | Effects of ABT-773 on the PK of Theophylline | N = 18 | Study completed | No clinically significant drug interaction was observed. |
| M00-155 | Healthy Adults | Effects of ABT-773 on the PK of Midazolam (CYP3A substrate) | N = 24 | Study completed | ABT-773 inhibited midazolam metabolism doubling midazolam AUC. Interaction smaller than interaction between clarithromycin and midazolam. |
| M00-156 | Healthy Adults | Effects of Rifampin (CYP3A inducer) on PK of ABT-773 | N = 18 | Study completed | Rifampin induced ABT-773 metabolism decreasing ABT-773 AUC by >90%. ABT-773 should not be given with any drug that might induce CYP3A. |
| TBD | Healthy Adults | Assessment of the Pharmacokinetic Interaction Between ABT-773 and Warfarin | TBD | Protocol TBD | R-warfarin is a CYP3A substrate and warfarin is a NTI drug. |
| TBD | Healthy Adults | Assessment of the Pharmacokinetic Interaction Between ABT-773 and Digoxin | TBD | Protocol TBD | Digoxin is a Pgp substrate and a NTI drug. |

Drug Interaction Program

As indicated in the Phase 1 clinical overview, further studies in special populations and drug-drug interaction assessments will be conducted. Preliminary pharmacokinetic data are available from five drug interaction studies. Because ABT-773 will be administered to women who rely upon oral contraceptives for birth control, a study was conducted to determine whether ABT-773 affects the pharmacokinetics of the components of a commonly-used combination oral contraceptive product (Ortho-Novum 1/35). Because ABT-773 will be co-administered with

theophylline in bronchitis patients, a study was conducted to determine whether ABT-773 affects the pharmacokinetics of theophylline. Because ABT-773 is known to be a substrate and inhibitor of the cytochrome P450 3A4 isoform subfamily (CYP3A4) in vitro, three clinical drug-drug interaction studies suggested in FDA Guidance on in vivo drug metabolism/drug interaction were conducted. Because ABT-773 is a CYP3A4 substrate, we have examined the effects of the CYP3A4 inhibitor, ketoconazole, and the inducer, rifampin, on the pharmacokinetics of ABT-773. Because ABT-773 may be an inhibitor of CYP3A4 in vivo, we have examined the effects of ABT-773 on midazolam pharmacokinetics. Preliminary pharmacokinetic and safety data are also available from a special population study in Japanese subjects.

In addition to these five completed drug-drug interaction studies, the effects of ABT-773 on the pharmacokinetics of warfarin and digoxin will be examined. A special population study to examine the effects of mild and moderate hepatic impairment (Child-Pugh) on ABT-773 is ongoing. Because no more than 10% of ABT-773 is excreted in the urine, a reduced-design study to examine the effects of severe renal impairment (creatinine clearance: 10-29 ml/min) on ABT-773 will be conducted. An additional special population study will be conducted to examine the effects of age and gender on ABT-773 pharmacokinetics.

G. Clinical Trial Program

G.1 Clinical Trial Program SWOT Analysis

Strengths, weakness, opportunities and threats regarding the clinical program for ABT-XXX are discussed below:

| Table G.1 SWOT Analysis (Strengths/Weaknesses/Opportunities/Threats) | | |
|----------------------------------------------------------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| CATEGORY | ITEM (Probability/Impact) | STRATEGY |
| Strengths | <ol style="list-style-type: none"> 150 mg QD dose should minimize side effects and provide sufficient exposure for efficacy. Complete Pharyngitis, and ABECB comparative Phase III studies by 2Q, 2001, and concentrate thereafter on CAP and ABS. | <ol style="list-style-type: none"> Two studies using this dose, two studies comparing it to higher dose for further evaluation in CAP and sinusitis. Prepare all documentation for NDA/regulatory filings before CAP and sinusitis studies complete. |
| Weaknesses | <ol style="list-style-type: none"> AE profile – GI, taste, at 300mg significantly higher than clari 500mg BID. Completion of CAP and sinusitis studies comparing 150 QD and BID may not occur by 2Q, 2001, delaying start of other pivotal studies. Further changes/amendments to protocols. Fail to enroll CAP and sinusitis patients early in season for Phase III trials starting 3Q, 2001. | <ol style="list-style-type: none"> Use lower dose (150 mg QD). Increase numbers of sites, work with experienced CROs, use sites in Eastern Europe. Monitor data carefully and stop study if significant trend towards one arm. Amendments will not be finalized until studies are initiated with original protocols. Increase numbers of sites, work with experienced CROs, use sites in Eastern Europe. Add South American sites if needed (2002). |
| Opportunities | <ul style="list-style-type: none"> Claim for resistant organisms. | <ul style="list-style-type: none"> Conduct studies in geographical locations where resistant bacteria are prevalent. Use central labs wherever possible. |
| Threats | <ul style="list-style-type: none"> Studies being done by other sponsors. | <ul style="list-style-type: none"> Pay appropriately; maximize contact with investigators. Hold successful investigator meetings and use retainer fees if necessary. |

G.2 Clinical Trials

Table G.2.a lists all the planned and proposed clinical trials for ABT-773:

| Table G.2.a: Clinical Trials (Phase 2-3) | | | | | |
|------------------------------------------|-------|-----------------------------------------------------------------|-------------|-------------|-------------------------------------------------------------------------------------------------------------------------------------------|
| STUDY | PHASE | OBJECTIVE/ PURPOSE OF STUDY | # OF PTS | FUNDED ? | LIKELIHOOD OF ACHIEVING OBJECTIVE/COMMENTS |
| M00-219 | III | CAP; 773 150 QD vs. 150 BID | 800 | Yes | 11/2000 - 4/2001, 50% likely to finish on time. |
| M00-216 | III | ABECB; comparing AZI vs. 773 | 600 | Yes | 11/2000 - 4/2001, 100% likely to finish on time. |
| M00-217 | III | ABECB; comparing Levo vs. 773 | 500 | Yes | 11/2000 - 4/2001, 100% likely to finish on time. |
| M00-225 | III | Sinusitis; 773 150 QD vs. 150 BID | 600 | Yes | 11/2000 - 4/2001, 50% likely to finish on time. |
| M00-223 | III | Pharyngitis; comparing penicillin (250 mg TID) vs. ABT773 | 520 | Yes | 11/2000 - 4/2001, 100% likely to finish on time. There is some chance that it will not meet FDA standards of >85% at 30 days. |
| M00-222 | III | Pharyngitis; comparing penicillin (500 mg TID) vs. ABT773 | 520 | Yes | 11/2000 - 4/2001, 100% likely to finish on time. |
| M00-221 | III | CAP; comparing Levo vs. 773 | 450 | Yes | 09/2001 - 04/2002, 50% likely to finish on time. |
| M00-220 | III | CAP; comparing Amoxicillin vs. 773 | 500 | Yes | 09/2001 - 04/2002, 50% likely to finish on time. |
| M00-226 | III | Sinusitis; comparing quinolone TBD vs. 773 | 450 | Yes | 09/2001 - 04/2002, 75% likely to finish on time |
| M00-218 | III | Sinusitis; comparing Augmentin vs. 773 | 500 | Yes | 09/2001 - 04/2002, 75% likely to finish on time |

Phase 2

In Phase 2a study M98-967, subjects with ABECB were treated with 100 mg TID or 200 mg TID dosing regimens which resulted in high clinical and bacteriological cure rates (see Section 9.3).

Three Phase 2b studies (see Section 9.4) conducted in both the US and EU investigating ABT-773 once daily doses have been completed:

- M99-054 - Community-acquired pneumonia (300 mg or 600 mg once daily for 7 days)
- M99-053 - Acute bacterial sinusitis (150 mg, 300 mg, or 600 mg once daily for 10 days)
- M99-048 - Acute bacterial exacerbation of chronic bronchitis (150 mg, 300 mg, or 600 mg once daily for 5 days)

Phase 3

The Phase 3 program consists of trials originating in either the United States or Europe comparing the safety and efficacy of ABT-773 in the proposed indications as described below.

- Community Acquired Pneumonia (total n ~ 1200 for ABT-773 arms)
 - M00-221 - One pivotal United States Phase 3, Controlled Study
 - M00-219 - One pivotal United States Phase 3, 2 Dose Study
 - M00-220 - One supportive European Phase 3, Controlled Study
- Acute Bacterial Exacerbation of Chronic Brouchitis (total n ~ 500 for ABT-773 arms)
 - M00-216 - One pivotal United States Phase 3, Controlled Study
 - M00-217 - One supportive European Phase 3, Controlled Study
- Acute bacterial sinusitis (total n ~ 1000 for ABT-773 arms)
 - M00-226 - One pivotal United States Phase 3, Controlled Study
 - M00-225 - One pivotal United States Phase 3, 2 Dose Study
 - M00-218 - One supportive European Phase 3, Controlled Study
- Pharyngitis (total n ~ 500 for ABT-773 arms)
 - M00-223 - One pivotal United States Phase 3, Controlled Study
 - M00-222 - One supportive European Phase 3, Controlled Study

Strategy of Clinical Program

A global clinical development program has been implemented intended for world-wide registration. An estimated total of 5,500 subjects will be enrolled in the Phase 3 clinical program including both study drug and comparator. Approximately 3,500 subjects world-wide will be available for the efficacy evaluation of ABT-773. An estimated total of 5,300 subjects will be available for the safety evaluation of ABT-773 including Phase 1/2/3 data.

1. ABT-773 Dose Selection for Phase 2a Study in ABECB (M98-967)

ABT-773 is a potent antibacterial agent with *in-vitro* activity against community-acquired respiratory pathogens including *S. pneumoniae*, (including penicillin-resistant and macrolide-resistant strains; PRSP and MRSP) *H. influenzae*, *S. pyogenes*, *M. catarrhalis* and atypical organisms including *Mycoplasma spp.*, *Chlamydia spp.* and *Legionella spp.* It also has activity against anaerobic gram-positive bacteria found in the normal upper respiratory tract and the bowel flora.

In addition, ABT 773 has been shown to demonstrate *in vivo* efficacy in animal model pulmonary infection studies against these prevalent respiratory pathogens.

The highest MIC exhibited to ABT-773 among respiratory pathogens (including PRSP/MRSP) is that of *H. influenzae*. The MIC₉₀ ranges from 2-4 µg/ml. In rat lung efficacy studies the CFU reduction in rat lung (2 log₁₀ -3 log₁₀) was exhibited by an AUC of 2.4-9.4 µg•hr/ml when the drug was administered as a BID regimen.

Unformulated drug was delivered in capsules as QD, BID and TID regimens in dose-escalating single and multiple dose studies (100 mg QD as lowest dose) in order to evaluate the PK properties and safety profile, and to determine the dose regimen for the Phase 2a study.

The three key factors considered in selecting the dose and frequency of dosing for the Phase 2a study from the Phase 1 dose-escalating studies were; the AUC range necessary to treat *H. influenzae* in animal model studies, the safety profile of the drug, and the goal to simulate an extended release profile for eventual once daily dosing.

Based on these considerations 100 mg TID and 200 mg TID dose regimens were selected for Phase 2a study M98-967. The mean AUCs for these regimens determined in Phase 1 studies were approximately 4.1 µg•hr/ml and 14.9 µg•hr/ml, respectively.

2. Dose Selection for Phase 2b Studies ABECB (M98-048), ABS (M98-053) and CAP (M98-054)

In several Phase 1 studies the mean AUC for 300 mg QD (3 x 100 mg capsules) ranged from 4.8-8.0 µg•hr/ml. The mean AUC values for the QD regimen were higher in all four Phase 1 studies than for TID regimen, and additionally, in one Phase 1 cross-over study (5.9 vs. 4.1 µg•hr/ml) due to some extent of diurnal variation in absorption.

The efficacy/safety results of 100 mg TID (M98-967) were excellent. The clinical and bacteriological cure rates were both 98% and adverse events were low with the exception of 11% diarrhea. The study indicated that 100 mg TID is an effective dose in ABECB in terms of clinical and bacteriological outcomes and has an acceptable safety profile. Pharmacokinetic data from a subset of subjects in this study indicated that the mean AUC for this regimen was 5.5 µg•hr/ml. Based on these results, 300 mg QD was selected as the middle dose for the Phase 2b trials (a preferred regimen over a TID regimen for patient compliance) since the 100 mg TID had demonstrated acceptable efficacy/safety and the QD regimen provided greater exposure than the TID regimen (plasma mean AUC values of 4.1 and 5.9 µg•hr/ml, respectively) as discussed

above. In addition, the 300 mg dose administered QD had a mean C_{max} value of 0.9 $\mu\text{g/ml}$, which together with the exposure outlined above, provides adequate coverage for bactericidal activity against PRSP/MRSP with MIC_{90} of 0.12.

Phase 2b studies were initiated with an immediate release tablet after multiple prototype extended release tablets failed to yield AUC values similar to that of the immediate release capsule and did not exhibit the desired extended release profile. Therefore, 150 mg immediate release tablets were manufactured and demonstrated to be bioequivalent to capsules (150 mg x 2 tablets vs 100 mg x 3 capsules) and were used in all three Phase 2b studies.

The 300 mg QD middle dose was bracketed in two of the dose-ranging Phase 2b studies (ABECB and ABS) with 150 mg and 600 mg doses to explore the optimal efficacy and safety range of the drug. In CAP, only 300 mg and 600 mg QD doses were used.

3. Dose Selection for Phase 3 Studies

The efficacy (clinical/bacteriology) data from the Phase 2b studies indicated that 150 mg, 300 mg and 600 mg were effective in treating subjects with ABECB (5 days) and ABS (10 days). The 300 mg and 600 mg were both effective doses to treat CAP (7 days) subjects.

The safety data indicated that all doses studied did not yield any clinically significant safety abnormalities as far as elevation of liver enzymes or QT prolongation are concerned. The 300 mg and 600 mg doses exhibited moderate amounts of taste disturbance and GI side effects, which were mainly diarrhea, nausea and vomiting.

Overall eradication of *S. pneumoniae* was excellent in all three studies. The data suggested that there was no apparent relationship between MIC and eradication or persistence of the isolates in the three trials, as would be expected with a susceptible population. There were no significant differences in eradication of *S. pneumoniae* between the dose groups in each of the trials and no evidence of development of resistance or of an increase in MIC in persistent isolates. Four MRSP isolates (2 *mef/2 erm*) were eradicated at the 150 mg dose in the ABECB study.

Regarding *H. influenzae*, overall eradication rates were high in ABECB and CAP. There were too few isolates in ABS to draw any conclusions. The data suggested that eradication or persistence was not predicted by the MIC value again consistent with a susceptible population where occasional persistent isolates are seen. Differences in eradication of *H. influenzae* were not significant between the dose groups in the three studies. For *H. influenzae*, 17/18 (94%) isolates were presumed eradicated in the ABECB study in the 150 mg arm of the study. The number of

H. influenzae isolates in the ABS study were too few to reach a meaningful conclusion (3/5) of presumed eradication.

There were no statistically significant differences between the 150 mg and 300 mg arms of the clinical outcome in ABECB and ABS studies, and the confidence intervals suggested they were equivalent in clinical outcome. However, 150 mg was tolerated better as far as taste disturbance and GI adverse events.

ABECB/Pharyngitis - Since both confidence intervals and statistical tests suggested that 150 mg and 300 mg dose groups were similar in both clinical and bacteriological outcome, it was decided to proceed into Phase 3 for ABECB indication with two studies using a 150 mg QD dose for 5 days. It was also decided to use this dose in the pharyngitis/tonsillitis studies, based on excellent *in vitro* activity of this drug against *S. pyogenes*, including macrolide resistant strains.

ABS - Excellent clinical activity was demonstrated in the 150 mg arm. Due to low pathogen recovery rate in this study, it was decided to conduct a double-blind Phase 3 two-dose study comparing 150 mg QD vs 150 mg BID (with sinus punctures) in lieu of the open single dose Phase 3 study as recommended in the FDA guidance document. After selecting the most appropriate dose from this initial study, based on clinical efficacy/bacteriology and safety outcomes, two additional Phase 3 pivotal studies will be performed. For this first study, 150 mg BID was selected since this regimen has been shown to have a lower C_{max} compared to 300 mg QD, thus potentially resulting in less taste disturbance and possibly lower GI side effects. In addition, the AUC values (3.9-5.8) obtained in Phase 1 studies are within AUC values of 150 mg and 300 mg QD, two doses that were shown to be effective in this indication.

CAP - For this indication, it was decided to conduct a double-blind Phase 3 two-dose study comparing 150 mg QD vs 150 mg BID in lieu of the open single dose Phase 3 study as recommended in the guidance document. The 150 mg QD dose was included, although it was not evaluated in the Phase 2b study, it exhibited efficacy in the ABECB and ABS Phase 2b studies. The 150 mg BID was selected due to its potentially lower taste disturbance and GI adverse event profile compared to 300 mg QD. After selecting the most appropriate dose from this initial study, based on clinical efficacy/bacteriology and safety outcomes, two additional Phase 3 pivotal studies will be performed.

4. Selection of comparators for Phase III studies

Selection of comparators were based on input from PPD, AI and affiliate marketing groups, medical and regulatory members of PPD and AI and finally input from three regulatory agencies

in Europe (UK, France and Germany) as well as US FDA Anti-Infective Division. A total of 10 studies are planned to be conducted. Two studies in ABECB, one in Europe and one in US. The European study will be vs Levofloxacin and US study vs Azithromycin. Both drugs have major market shares in this indication, Azithromycin in US and Levofloxacin is gaining momentum in Europe.

There are three planned studies for ABS, including two comparative studies vs Augmentin. And the two dose ABT 773 study. Augmentin is a key product in this indication both in US and Europe. In all probability, for the European study, Augmentin will be replaced with a quinolone. The plan will be finalized shortly.

The plan for acute streptococcal pharyngitis (ASP) calls for two studies against the standard treatment ; Penicillin V. 500mg tid, one in US and the second in Europe.

The CAP plan calls for three studies, the first, a two dose study of ABT 773 followed by a comparative study in Europe vs Augmentin and a comparative study in US vs Levofloxacin. Both products are used in this indication and it will be important to compare the efficacy/safety profile of ABT 773 with these agents. In all probability, for the European study, Augmentin will be replaced with a Amoxicillin 1gm TID. The plan will be finalized shortly

H. Chemistry, Manufacturing and Controls

H.1 Chemistry, Manufacturing and Controls SWOT Analysis

| Table II.1 SWOT analysis (Strengths/Weaknesses/Opportunities/Threats) | | |
|-----------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| CATEGORY | ITEM (Probability/Impact) | STRATEGY |
| Strengths | Over 3600 kg of bulk drug have been successfully manufactured with overall yields improving from 21% to greater than 30%. Excellent progress on improving costs of bulk drug, currently less than \$6500/kg with target of \$2500/kg at launch.. | Produce required development quantities of bulk drug to meet the cost targets at launch. Continue to obtain yield improvements through process work and manufacturing volume. |
| | Registration runs incorporated qualifying vendors for intermediates that will drive further bulk drug cost reductions and assure availability of bulk drug. | Obtain Regulatory approval (both AI and FDA) to identify intermediate step 5 as a starting material to allow for further process improvements at the earlier steps of manufacturing. |
| | Formulation is a familiar technology, immediate release QD formulation manufactured by wet granulation. | Continue to decrease cost of intermediates through use of three to four vendors. |
| | Two sites of final product manufacturing (one in the U.S. and one in AI) at launch. | Utilize an integrated scale-up program with both PARD and IDC to assure that a single formula/process will be used worldwide. Two manufacturing sites provides back up support to AI and future potential back up to the U.S. |
| Weaknesses | Current bulk drug process requires 9 steps and high cost side chain which may limit potential cost improvements beyond launch. | Process development underway to evaluate optimized/new chemistry routes and potential to simplify the manufacturing process. |
| | ABT-773 has a bitter after taste as a result of excretion into the saliva that cannot be masked in the formulation. This is the most frequent adverse event identified in the Phase II clinicals. | The 150 mg tablet minimizes after taste problems however, this will be a challenge in formulating a pediatric product.. |
| | Phase III clinicals and NDA stability will be performed using an intermediate scale formulation. | A bioequivalency study will be performed linking the 10L bench formulation used in the Phase II clinicals, to the 300L intermediate formulation used in the Phase III clinicals, to the commercial scale (1200L U.S. and 600L U.K.) formulations. |
| Opportunities | Due to Regulatory issues, there will not be a back-up site for the U.S. at launch. | Evaluate a separate project to obtain second site approval for the AI site to provide back up to the U.S. |
| | Experience with bulk drug substance in terms of physical properties will allow us to develop specifications to improve consistency in formulation. | Particle size analysis is ongoing to provide data to support defining physical specifications by January 2001. |

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|----------------|---------------------------------------------------------------------------------------------------------------------------------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| | Obtaining regulatory approval for definition of step 5 as starting material will provide more opportunity for process improvements to reduce COGs | SPD, PPD and AI are collaborating on a solid data package to defend our step 5 starting material definition. An end of Phase II CMC meeting will be scheduled at the end of 2000 with FDA to discuss our strategy. Early discussions with the U.K. regulatory agency were optimistic. |
| Threats | Having one site for bulk drug can always carry risks. | A second site (Puerto Rico or Italy) will be considered in 2001 based on marketing forecast and capacity. |

H.2 SPD/PPD Chemical Sciences

SPD has made significant breakthroughs since 1997 to bring the cost of drug from \$30M to \$6.5M. Further reductions are expected by reducing the cost of the PQC side chain (competitive bidding among vendors), reducing the number of process steps, reducing the number of intermediate isolations, and increasing the batch size. An ongoing analysis of the assembly process is being made to evaluate the efficiencies gained in various steps in the process, and/or outsourcing a series of steps. The cost of drug during the filing year, 2002 is anticipated to be about \$2500/Kg.

Bulk Drug Requirement

Project: AB11-773 Adult Tablet

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| | | | | | | | |
|-------------|------------------------------------------|-----------------|----------|-------------------|-------------|----------|-----------|
| | | | | Inventory Balance | | | |
| End Q4 1999 | | | | 964kg | | | |
| | | | | | | | |
| | | Bulk Deliveries | | Usage (Quantity) | | | |
| | | Description | Quantity | Clinical | Formulation | Scale-Up | Inventory |
| Q1 2000 | Campaign 6, pre-NDA run | 321.2 kg | 321.2kg | | | | 1285.2kg |
| Q2 2000 | Campaign 7, 8, 9 NDA runs | 1008.9 kg | | | 1008.9kg | | 2294.1 |
| Q3 2000 | Campaign 10, NDA run, Cam 11,12 dev runs | 1029.9 kg | | | 1029.9 kg | | 3324kg |
| Q4 2000 | Campaigns 13, 14 development runs | 670 kg | | | 670 kg | | 3994kg |
| Q1 2001 | Campaign 15, 16 development runs | 670 kg | | | 670 kg | | 4664kg |
| Q2 2001 | Shut down for facility upgrade | | | | | | 4664kg |
| Q3 2001 | Campaign 17 | 335 kg | | | 335 kg | | 4999kg |
| Q4 2001 | Campaign 18,19 | 670 kg | | | 670 kg | | 5669kg |

Lead Time (request to delivery; weeks) 6 mo

Comments:

Schedule B ABT-773 Bulk Drug Usage – Tablet Formulation

| Task | Start | Finish | Task Use |
|----------------------------------------------------------------|--------------|---------------|-----------------|
| 1 10L Formulation Prototypes | Nov/09/98 | Jun/30/99 | 107.8 |
| 12 75L Process Dev't/Bulk Drug Eval (24 runs, 200 kg) | Aug/23/99 | Oct/01/99 | 151.0 |
| Clinical Re-Supply PH II | Sep/08/99 | Sep/08/99 | 5.4 |
| 14 Dissoln Method Justification Biostudy- Clin Mfg - 3 runs | Oct/04/99 | Nov/15/99 | 24.0 |
| 16 Process Dev/Bulk Drug Eval 75L Pt2 (8 runs, 66.4 kg) | Nov/16/99 | Dec/10/99 | 59.0 |
| 18 UK Site/2nd Process Verification 25L (33 kg) | | | |
| Batches 1-3 | Dec/01/99 | Jan/31/00 | 10.0 |
| Batches 4-6 | Feb/01/00 | Mar/13/00 | 10.0 |
| Batches 7-10 (two batches) | Mar/14/00 | Oct/11/00 | 13.2 |
| 22 Proc. Supportive Dev. 75L Pt3 (16 runs-rep. Scale; 132.8kg) | Dec/13/99 | Feb/04/00 | 132.8 |
| 24 75 L Bulk Drug Eval Pt 3 (10 runs; INCL cmpn 6 re-work) | Feb/01/00 | Dec/01/00 | 84.7 |
| 26 Process Dev 300L (4 runs; 133.2 kg) | Jan/10/00 | Feb/04/00 | 130.0 |
| Phase III Clin Supply mfg, 75L Gral, 300 mg white, 62-329-AR | Mar/14/00 | Mar/21/00 | 16.1 |
| 75L, 200 mg IR-D, lot 65-362-AR | May/22/2000 | Jul/14/2000 | 24.1 |
| 28 Process Dev Pre-NDA (11 runs; 366.3 kg) | Feb/07/00 | Apr/14/00 | 364.0 |
| 300L Gral, 300 mg IR-D ScaleUp Lot; 65-015-4Q | May/31/2000 | Jun/13/2000 | 64.2 |
| 150 mg switch | | 0 | |
| 150 mg factorial compression study | | | 24.0 |
| 150 mg tablet coating study | | | 56.0 |
| 33 Mfg. NDA Runs - 1 Strength (4 lots/10 runs; 333kg) | | | |
| 34 NDA Lot 1 (Abbott; Cmpgn 7-rework) | ? | Jul/17/00 | 66.6 |
| NDA Bio Lot 2 (ChemiSpa), Phase III supplies; 66-018-4Q | Jul/31/00 | Aug/11/00 | 66.6 |
| NDA Lot 3 (Uquifa); 67-021-4Q | Sep/25/00 | Oct/06/00 | 66.6 |
| NDA Lot 4 (Taisho) | Sep/25/00 | Oct/06/00 | 66.6 |
| 39 Process Verification 65 L (146 kg) | Feb/07/00 | Sep/29/00 | |
| Batches 1-6 | Oct/18/00 | May/31/00 | 50.0 |
| Batches 7-12 | Jun/01/00 | Jul/31/00 | 50.0 |
| Batches 12-15 (two batches) | Aug/01/00 | Mar/26/01 | 35.0 |
| Biobatch, 65L vs 300L (20 kg) | May/01/01 | May/31/01 | 20.0 |
| 46 Process Dev 1200 L (4 runs, 532 kg) +1 run?= 665kg | Jan/22/01 | Mar/05/01 | 665.0 |

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| | | | | |
|----|------------------------------------------------------------|-------------|------------|---------|
| 50 | 1200L Def Bio & Registration Lots (3 lots, 4 runs; 532 kg) | Mar/06/01 | Jul/09/01 | 532.0 |
| | Definitive Biostudy, 300L vs 1200L | May/29/01 | Jun/25/01 | |
| 57 | 75L Supportive Dev (For the 1200L, 20 runs; 166 kg) | Jan/17/01 | Aug/23/01 | 166.2 |
| 58 | 300L Supportive Dev (For the 1200L, 5 runs; 166.5 kg) | Jan/17/01 | Aug/23/01 | 167.0 |
| 60 | Demonstration Lot 1200 L (3 runs; 399 kg) | Apr/01/02 ? | Jun/21/02 | 399.0 |
| 65 | Process Transfer(i) 600L U.K. Site (3X 83 kg= 249kg) | Apr/19/01 | May/18/01 | 249.0 |
| | Process Transfer (ii) 600L U.K. (2x 83kg= 166 kg) | Jun/27/01 | Jul/24/01 | 166.0 |
| | Bio Batch UK | Sep/13/01 | Oct/02/01 | 83.0 |
| | Batch Analysis, 2 lots; 2x 83 kg | Sep/05/01 | Sept/27/01 | 166.0 |
| | Demo Batch 1 UK; (1 lot, 3 runs= 333 kg) | Apr/04/02 | May/03/02 | 333.0 |
| | 1200L Validation Runs (3 Lots, 3 Runs ea; 1197 kg) | Jun/05/02 | Aug/28/02 | 1200.0 |
| | Launch | | 1Q2003 | |
| | Total Bulk Drug Usage | | | 5823.90 |

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Schedule C

Bulk Drug Cost Status

| | Current Average Cost (000) | Projected Commercial Cost (000) |
|-----------------|-------------------------------------------|------------------------------------------------|
| Materials | 3.7 | 1.3 |
| Labor/Equipment | 2.4 | 1.05 |
| Process Support | 0.4 | .15 |
| Total | 6.5 | 2.5 |

| Event | Year | Project Average Cost/Kilo | |
|-----------------------|-------------|----------------------------------|-------------------------|
| | | DDC | Actual/Projected |
| DDC | 97 | 150 | 150 |
| | 98 | 30 | 30 A |
| Phase IIb | 99 | 10 | 10 A |
| Phase III start | 00 | 7.5 | 6.7 A |
| | 01 | 5.0 | 5.0 P |
| Filing | 02 | 4.0 | 4.0 P |
| Launch | 03 | 2.5 | 2.5 P |
| Dose Projection | | 150mg/Day | 150mg/Day |
| Cost/Dose/Day Bottle | | \$0.4218/Day | \$0.4218/Day |
| Cost/Dose/Day Blister | | \$0.5702/Day | \$0.5702/Day |

II.3 PARD/IDC

An immediate release 150 mg formulation has been selected for commercial development of ABT-773. The formulation was reduced in size from the original 300 mg tablet previously targeted for development. The formula and process will be global with respect the excipients and an integrated scale up program with the IDC will assure that a single formula/process (with common packages) will be used throughout the world. The CMC working group continues to review needs on the bulk drug for clinical use and process development as the program develops. Common specifications for the bulk drug substance and the formulation remain a goal of the CMC development group.

H.4 Manufacturing

ABT-773 tablets will be manufactured in AP16 for PPD domestic supply, and as a back-up facility for AI supply. Queenborough, UK will manufacture for AI supply, including Japan. There will be a common, global formula (0.3g tablet weight, with pale pink coating). The only possible exception will be if we need to develop different codes of bulk drug for PPD and AI.

The manufacturing process is a conventional tableting process. In AP16, ABT-773 will be granulated in the 1200L Gral, in 3 runs, then blended (75 cuft), compressed and coated (60" Accelacoater) as 150mg tablets. In the UK, ABT-773 will be granulated in the 600L TK Fielder, in the 3 runs, then blended and coated as 150mg tablets. The Japanese product will be manufactured with the same granule, to a lower compression weight, if Japan proceeds with 100mg tablets. This strength is yet to be determined. Capacity reviews at both plants indicate that there is sufficient capacity, including upside demand. The tablets will be packaged into 30# bottles, and peelable blister (Hospital Unit Dose) and push-through blister (compliance pac)

H.5 Patent Issues

U.S. Patent 5,866,549 claiming ABT-773 and its analogs issued on February 2, 1999. The patent will expire on September 4, 2016. Three divisional applications claiming related compounds in the series are pending prosecution in the United States Patent and Trademark Office. The patent applications corresponding to the issued patent and pending patent applications have been filed in more than forty countries outside the US, thus providing extensive worldwide patent protection for the compound

I. Non-Clinical

I.1 Non-Clinical SWOT Analysis

Strengths, weakness, opportunities and threats regarding the non-clinical program for ABT-773 are discussed below:

| Table I.1 SWOT Analysis (Strengths/Weaknesses/Opportunities/Threats) | | |
|----------------------------------------------------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| CATEGORY | ITEM (Probability/Impact) | STRATEGY |
| Strengths | <p>All key toxicology studies have been initiated or completed.</p> <p>ABT-773 is active against penicillin-resistant and macrolide-resistant <i>S. pneumoniae</i> including Erm^{AM} and Mef phenotypes; it does not induce MLS_B (macrolides, lincosamides and streptogramin B) resistance.</p> | <p>Complete Tox package for NDA early on.</p> <p>Key positioning in the marketplace as a safe, effective antibiotic that treats resistant organisms and does not induce resistance.</p> |
| Weaknesses | <p>Tox: Relatively small safety margins between the no-effect level exposures and clinical exposure.</p> <p>Micro: Pharmacokinetic profile based on traditional profiles, may not support the 150mg dose.</p> <p><i>H. flu</i> MIC 2-4 is a high MIC to achieve by blood levels.</p> | <p>Safety data is available from clinical studies.</p> <p>Ribosome kinetics are now being studied as a means of providing crucial support to our decision to proceed with 150 mg. A plan has been established to devise a mechanistic rationale for the 150 mg program that goes beyond the traditional two-factor paradigm i.e. concentration & MIC and establishes this concept as the new in vitro paradigm to predict efficacy.</p> <p>Demonstrate clinical activity in <i>H. flu</i> and use tissue level data if available.</p> |
| Opportunities | <p>Micro: Kinetic and binding studies have shown that this ketolide associates very rapidly with susceptible ribosomes and dissociates very slowly. ABT-773 also appears to be capable of lower affinity binding for methylated streptococcal ribosomes</p> | <p>Further characterization of this additional binding and its role in anti-bacterial activity is being investigated.</p> |
| Threats | <p>Testicular effects and impaired fertility in the rat Segment I study.</p> | <p>Fertility evaluation should be included in the clinical program.</p> |

1.2 Toxicology

All key toxicology studies for ABT-773 have been initiated or completed. All acute and genetic toxicity studies, two-week toxicity studies in rat and monkey, one-month toxicity studies in rat and monkey, a three-month study in rat, and embryonic and fetal developmental (Segment II) studies have been completed. A three-month study in monkey, a juvenile toxicity study in rat, a fertility and early embryonic development (Segment I) study in rat, a peri- and postnatal (Segment III) study in rat and an antigenicity study in guinea pig are ongoing.

In rats, increased mortality, decreased body weight gain and food consumption, and manifestations of toxicity in the liver, kidney, lung, testes and epididymides were observed at dosages of 180 and 160 mg/kg/day in the one-month and three-month study, respectively. Mild and reversible toxicity of these organ systems was seen at 60 mg/kg/day. The no-toxic-effect level (NTEL) in the three-month rat study was 20 mg/kg/day ($AUC = 11-25 \mu\text{g}\cdot\text{hr}/\text{ml}$). The mean plasma exposure of ABT-773 in humans is expected to be 2-5 $\mu\text{g}\cdot\text{hr}/\text{ml}$ (150-300 mg/day dose) and thus the NTEL in animals are approximately 2-13 times higher than anticipated human exposures.

In monkeys, emesis was observed in a dose-related manner. Decreased body weight gain and food consumption, and manifestations of toxicity in the liver, kidney, bone marrow and lymphoid tissues were observed at a dosage of 200/140 mg/kg/day in the one-month study. Preliminary data showed that liver toxicity was also observed at dosages of 50 and 100 mg/kg/day in the three-month study. The no-toxic-effect level (NTEL) in the three-month monkey study was 25 mg/kg/day ($AUC = 7-10 \mu\text{g}\cdot\text{hr}/\text{ml}$); exposures at this dosage are approximately 1.5-5 times higher than anticipated human exposures.

Embryonic and fetal developmental studies conducted showed no fetal malformation at dosages up to 80 mg/kg/day in rats and 100 mg/kg/day in rabbits. In an ongoing fertility and early embryonic development study, preliminary data showed adverse effects on fertility at dosages of 60 and 180 mg/kg/day. Recovery of this effect on fertility was seen at 60 mg/kg/day, but not at 180 mg/kg/day. This finding agrees with the testicular effects seen in the three-month rat study. Clinical implications of this finding is not known, although similar findings have been reported with other macrolides. Preliminary data of the peri- and postnatal study showed decreased pup growth and development at 80 mg/kg/day; these effects were believed to be secondary to reduced weight gain of dams during gestation.

Genetic toxicology studies conducted with ABT-773 included Ames assay, mouse lymphoma assay, *in vitro* cytogenetics assay and *in vivo* mouse micronucleus assay. ABT-773 was not found to be genotoxic in any of these assays.

New impurities, not covered by the toxicology lot used for three-month studies, have been generated. Acute toxicity, genotoxicity and bioavailability studies are being conducted with these impurities to qualify their use in the clinical trials. Longer term toxicology testing will be done when the impurity profile for ABT-773 is determined (NDA runs).

1.3 Metabolism

Studies of the oral or intravenous single dose pharmacokinetics of ABT-773 have been performed in the rat, mouse, dog and monkey following single doses. These data suggested ABT-773 may possess a balanced pharmacokinetic profile similar to that of clarithromycin. ABT-773 exhibits sufficient plasma concentrations and tissue distribution to provide effective treatment *in vivo* for bacterial infections of upper and lower respiratory tract. The data from the study in dogs indicate that ABT-773 has a favorable oral pharmacokinetic profile with 51.3% absolute bioavailability from a simple capsule formulation and low animal-to-animal variability. ABT-773 has a half-life similar to that of clarithromycin in dogs (4.1 and 5.4 hrs, respectively), with a C_{max} of 0.88 µg/mL following an oral dose of 5 mg/kg.

[14 C] ABT-773 was found to undergo NADPH-dependent metabolism by liver microsomes from mouse, rat, dog, monkey and humans with wide interspecies variability in the rates of metabolism with monkey and rat exhibiting highest and lowest rates of metabolism, respectively. In all cases the major metabolite formed was an *N*-desmethyl derivative of ABT-773 (M-1). ABT-773 is rapidly cleared in rats after intravenous and oral administration and in dogs by oral administration. For both species, excretion is primarily by the liver with only a small fraction of the dose eliminated in the urine.

The *in vitro* studies across five species including man, suggest that ABT-773 shows a drug-concentration dependent decrease in protein binding. In man, for plasma concentrations above 3 mg/mL, plasma protein binding decreases with increasing total drug concentrations, presumably due to the saturation of the plasma binding sites. Because plasma concentrations of ABT-773 in humans are unlikely to exceed 2 mg/mL at clinically-relevant doses, the concentration dependence is not clinically important. In human plasma, [14 C] ABT-773 has a greater affinity for α_1 -acid glycoprotein (AAG) than for human serum albumin (HSA), and plasma protein binding at concentrations of 0.1 to 3 µg/mL was 95.5-95.6%.

ABT-773 is metabolized by human liver microsomes via CYP3A4. The drug also appears to be an inhibitor of CYP3A4 metabolism *in vitro*. The IC_{50} values obtained for the inhibition of CYP3A4-dependent metabolisms were in the same range as the total steady state peak plasma concentrations of ABT-773 (0.45 - 1.92 $\mu\text{g/mL}$) after 200-500 mg BID doses in humans. This indicates the potential for ABT-773 to inhibit the *in vivo* metabolism of coadministered drugs metabolized via CYP3A4.

I.4 Animal Safety Pharmacology

The pharmacology studies showed that ABT-773 has mild sedative actions with only modest, if any effects on other CNS, CV and/or GI functions at therapeutic to super therapeutic doses/plasma concentrations. These results indicate a minimal risk for marked adverse effects of this compound in clinical studies.

In *in vitro* cellular electrophysiologic studies, supratherapeutic concentrations of ABT-773 (at concentrations 10- and 100-fold above anticipated clinical therapeutic plasma levels) prolong the action potential duration of canine cardiac Purkinje fibers superfused with physiologic salt solutions. These *in vitro* studies likely overestimate the electrophysiologic effects of ABT-773 *in vivo* due to the extensive plasma protein binding of ABT-773. Prolongation of the Purkinje fiber action potential duration *in vitro* is dramatically reduced in the presence of plasma proteins; in the presence of 50% plasma, the dose-response curve for prolongation is shifted rightward, with significant prolongation observed only at 100-fold above the anticipated plasma levels of ABT-773.

When studied in the absence of plasma, the extent of action potential prolongation with ABT-773 is comparable to erythromycin, clarithromycin, and levofloxacin, and less than that of moxifloxacin when compared on the basis of plasma concentration multiples. Studies of M-1, the principal metabolite of ABT-773, demonstrate minimal effects on repolarization and only at high metabolite concentrations (100-fold excess of those found at clinically efficacious concentrations). An *in vivo* toxicology study with non-human primates reveals no significant prolongation of the QTc interval despite long-term exposure to supratherapeutic plasma levels of ABT-773.

I.5 Microbiology

In the past year, various external investigators have confirmed and expanded the early pre-clinical studies done at Abbott. The activity of ABT-773 against current respiratory tract

isolates including *S. pneumoniae* (macrolide susceptible and resistant), *H. influenzae* and *M. catarrhalis* was examined. An antibiotic surveillance study done by the University of Iowa found the MIC₉₀ of ABT-773 for *S. pneumoniae* (n=1601) was 0.03 µg/ml. Furthermore, the MIC₉₀ against low and high level macrolide resistant strains was 0.12 µg/ml. The highest ABT-773 MIC found in the study was 0.5 µg/ml (n=3). The activity of ABT-773 was found to be equivalent to azithromycin and superior to clarithromycin against *H. influenzae* and the ketolide was extremely potent against *M. catarrhalis*. Additional studies done by several other investigators confirmed these findings for respiratory pathogens. Kill kinetic studies with fastidious respiratory pathogens confirmed the bactericidal activity of ABT-773. The ketolide also showed extended post antibiotic effect compared to other macrolides for *S. pneumoniae* and *H. influenzae*.

Kinetic and binding studies have shown that this ketolide associates very rapidly with susceptible ribosomes and dissociates very slowly. ABT-773 also appears to be capable of lower affinity binding for methylated streptococcal ribosomes. Further characterization of this additional binding and its role in anti-bacterial activity is being investigated.

ABT-773 demonstrates *in vivo* efficacy equal or superior to available clinical therapeutics in animal studies against the most prevalent respiratory pathogens including *Streptococcus pneumoniae* and *Haemophilus influenzae*. Once daily (QD) therapy was as effective as twice daily (BID) therapy in treatment of rat pulmonary infections caused by *H. influenzae* and *S. pneumoniae*. ABT-773 also demonstrated efficacy against macrolide and penicillin resistant strains of *Streptococcus pneumoniae*. Efficacy was demonstrated against infections of salient anatomical locations including systemic (septic), inner ear (bullae), pulmonary, and skin abscess suggesting that ABT-773 penetrates into pulmonary tissue and intracellular locations while maintaining activity.

Addenda

- 1.0 Target Product Label**
- 2.0 Clinical Trial Program**
 - 2.1 Clinical Trials (Gantt Chart)**
- 3.0 Chemistry, Manufacturing and Controls**
 - 3.1 Milestones SPD/PPD Chemical Sciences Milestones (Gantt Chart)**
 - 3.2 PARD Milestones (Gantt Chart)**
- 4.0 Non-Clinical**
 - 4.1 Animal Toxicology and Metabolism Milestones (Gantt Chart)**
- 5.0 Project History**
 - 5.1 Expert Strategic Review Process - Summaries**
 - 5.2 Milestones**
 - 5.3 Highlights re: NCE**
 - 5.4 Historical Changes to ABT-XXX Target Product Profile**

Appendix 1

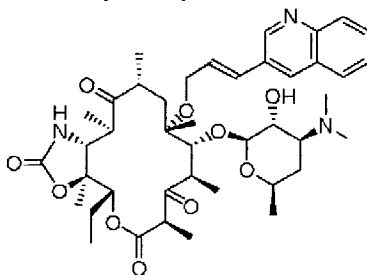
Target Product Label

ERADICATE® Filmtab®

(eradomycin tablets)

DESCRIPTION

Eradomycin is a semi-synthetic ketolide antibiotic. Chemically, it is 11-amino-11-deoxy-3-oxo-5-*O*-desosaminyl-6-*O*-[3'-(3''-quinoliny)-2'-propenyl] erythronolide¹. A 11,12-cyclic carbamate. The molecular formula is C₄₂H₅₃N₃O₁₀, and the molecular weight is 765.94². The structural formula is:



ethanol, and acetonitrile, and practically insoluble in water³.

ERADOMYCIN is available as immediate release tablets.

Each ovaloid film-coated ABT-773 tablet contains 150 mg of ABT-773 and the following inactive ingredients:

Cellulose, Microcrystalline, NF
Croscarmellose, Sodium, NF
Hydroxypropyl Cellulose NF
Magnesium Stearate, NF, Impalpable Powder
Silicon Dioxide, Colloidal, NF
Sodium Starch Glycolate, NF Powder
Starch, Pregelatinized, NF

Plus- coating solution (STILL BEING DEFINED):

iron oxides, hydroxypropyl methylcellulose, Polyethylene Glycol, Titanium Dioxide, sorbic acid⁴.

| <u>Study #</u> | <u>Comment</u> | <u>Start</u> | <u>End</u> | <u>Investigator/Contact</u> |
|-----------------|-----------------------------------------|--------------|------------|-----------------------------|
| ¹ NA | Confirm chemical name (IUPAC) | | | Z. Ma |
| ² NA | Confirmed | | | Z. Ma |
| ³ NA | Confirmed | | | Z. Ma |
| ⁴ NA | Info correct, how specific is required? | | | R. Schilling |

CLINICAL PHARMACOLOGY

ERADOMYCIN is rapidly absorbed from the gastrointestinal tract after oral administration⁵. The absolute bioavailability of 150-mg ERADOMYCIN tablets was approximately 77%^{6, 7, 8}. Food effects neither the rate nor extent of ERADOMYCIN absorption. Therefore, ERADOMYCIN tablets may be given without regard to food⁹.

In fasting healthy human subjects, peak serum concentrations were attained within 3 hours after oral dosing^{10, 11}. Steady-state peak serum ERADOMYCIN concentrations were attained in 3 to 4 days¹² and were approximately 1 µg/ml¹³ with a 150-mg dose administered every 24 hours. The pharmacokinetics of ERADOMYCIN are non-linear around the recommended dose of 150 mg administered once daily^{14, 15}. Typical pharmacokinetic parameters of ERADOMYCIN are shown in the following table.

Error! Bookmark not defined.

| PHARMACOKINETIC PARAMETERS (after 150 mg q 24 h) | | | | |
|-----------------------------------------------------|---------------------------------------|-------------------------------------------|-------------------------------------------|--------------------------------|
| T _{max} ¹⁶ (h) | T _{1/2} ¹⁷ (h) | C _{max} ¹⁸ (ng/ml) | C _{min} ¹⁹ (ng/ml) | AUC ²⁰ (ng·h/ml) |
| 2.7 ± 0.6 | | 855 ± 366 | 29 ± 13 | 5934 ± 2623 |

After a 150-mg tablet every 24 hours, approximately 7%²¹ of the dose is excreted in the urine as ERADOMYCIN. [No metabolite info presented; may have to defend]. [Does CYP3A have to be mentioned?]. The elimination half-life of ERADOMYCIN was about 6 to 8 hours²² with 150 mg administered every 24 hours.

The steady-state concentrations of ERADOMYCIN in subjects with impaired hepatic function did not differ from those in normal subjects²³; the steady-state concentrations of ERADOMYCIN in subjects with impaired renal function did not differ from those in normal subjects²⁴. [Will conduct study in elderly²⁵; will add comments about

- ⁵ M00-AAA Definitive bioassay
- ⁶ M00-BBB Single ascending IV, final, multiple rising dose + p.o.; assumes p.o. does not have to be final scale for 8/00 start
- ⁷ 100027
- ⁸ 100098
- ⁹ M00-AAA To be part of definitive bioassay
- ¹⁰ M97-716 3 hrs based on 716
- ¹¹ M00-AAA Confirmed with definitive bioassay
- ¹² M00-024 3-4 days based on 024 study; repeat only if diff. between 024 and 10-75L scaleup (M99-109)
- ¹³ M99-024 024 showed 1 µg/ml; repeat only if diff. between 024 and 10-75L scaleup (M99-109)
- ¹⁴ M99-018 Quantify non-linearity from study
- ¹⁵ M00-C00 150/300/600 mg single comparative study
If done, 018 would not be used; could also use M99-119 caucasian section
- ¹⁶ M99-016 Placeholder study; replace with M00-AAA
- ¹⁷ M99-016 Placeholder study; replace with M00-AAA
- ¹⁸ M99-016 Placeholder study; replace with M00-AAA
- ¹⁹ M99-016 Placeholder study; replace with M00-AAA
- ²⁰ M99-016 Placeholder study; replace with M00-AAA
- ²¹ M00-DDD C14 study, if low number (<20%), multiple dose will not be required
- ²² M99-024 6-8 hours based on 024 study; will also be based on M00-AAA
- ²³ M99-126 Protocol finished
- ²⁴ M00-FFF Low urine excretion will not require results of C14;
- ²⁵ M01-AAA Study in elderly; need final dosage form/dose

gender subanalyses but no specific studies]

Do we need adolescent study/section in label?

Distribution:

ERADOMYCIN distributes readily into body tissues and fluids. Volume of distribution?²⁶ Rapid distribution of eradomycin into tissues results in higher eradomycin concentrations in most target tissues than in serum (see table below) [will use either tissue and serum values or only ratios, whichever looks more favorable].

Error! Bookmark not defined.CONCENTRATION
(after 150 mg q 24 h)

| Tissue Type | Tissue (µg/g) | Serum (µg/mL) | T:S Ratio (µg/mL) |
|------------------------------------------|--------------------------|--------------------------|------------------------------|
| Tonsil ²⁷ | X.X | X.X | X.X |
| Lung ^{28 29} | X.X | X.X | X.X |
| Epithelial Lining Fluid ^{30 31} | X.X | X.X | X.X |
| Alveolar Macrophage ^{32 33} | X.X | X.X | X.X |
| White Blood Cells ³⁴ | X.X | X.X | X.X |
| Sinus Mucosa ³⁵ | X.X | X.X | X.X |
| Cerebral Spinal Fluid ³⁶ | X.X | X.X | X.X |
| Bronchial Mucosa ³⁷ | X.X | X.X | X.X |
| Sputum ³⁸ | X.X | X.X | X.X |

²⁶ M99-025

Absolute bioavailability study

²⁷ M99-142

Conte study; all raw data must be sent to Abbott, will forward to FDA (10/09)

²⁸ M99-142

²⁹ M99-007

Gottfried to execute; contact Gottfried for proposal

³⁰ M99-142

Conte study

³¹ M99-007

³² M99-142

Conte study

³³ M99-102

³⁴ M99-105

Samples being reassayed, orig. results relatively low

³⁵

TBD; not sure if pursuing

³⁶ M99-142

Conte study

³⁷

TBD; not sure if pursuing

³⁸

TBD; not sure if pursuing, ELF is better fluid

Microbiology:

ERADOMYCIN is a ketolide with concentration-dependent, bactericidal *in-vitro* activity against a wide range of aerobic and anaerobic gram-negative, gram-positive, and atypical microorganisms. ERADOMYCIN exerts its antibacterial action by binding to the 50S ribosomal subunit of susceptible microorganisms resulting in inhibition of bacterial protein synthesis^{39 40 41 42}. **ABT-773 binds to the ribosome rapidly, completely, and irreversibly⁴³. It appears that these ribosome-binding properties contribute to enhanced activity and lower selection of resistant mutants of gram-positive bacteria relative to other agents that act via the ribosome^{44 45 46 47}.** Eradomycin exhibits an in-vitro post-antibiotic effect (PAE), defined as the ability of an agent to sustain antimicrobial action after drug concentrations have fallen below the MIC.^{48 49 50}

The mechanism of action of ketolides including eradomycin is different from that of penicillins, cephalosporins, quinolones, aminoglycosides, and tetracyclines⁵¹. Therefore, **ERADOMYCIN may be active against pathogens that are resistant to these antibiotics^{52 53 54 55}. There is no cross-resistance between ERADOMYCIN and the mentioned classes of antibiotics⁵⁶.**

Macrolide resistance occurs principally by two main mechanisms of resistance. Production of ribosomal methylases, either inducible or constitutive, alters the ribosomal target inhibiting macrolide binding; an efflux mechanism pumps the antibiotic from within the microorganism. ERADOMYCIN has been shown in streptococcus to bind to methylated ribosomes^{57 58}, to not induce methylase resistance^{59 60}, and to bypass the efflux pump^{61 62}. **Thus ERADOMYCIN is active against macrolide resistant streptococci^{63 64 65}.**

Resistance to ERADOMYCIN in vitro develops slowly⁶⁶. Resistance to ERADOMYCIN in vitro occurs at a

| | |
|-----------------------------|--------------------------------------------------------|
| ³⁹ <u>99039</u> | Capobianco |
| ⁴⁰ <u>99017</u> | Zhong |
| ⁴¹ <u>99032</u> | Zhong |
| ⁴² <u>100077</u> | Zhong |
| ⁴³ <u>99049</u> | |
| ⁴⁴ <u>99068</u> | Liebowitz study (serial dilution) |
| ⁴⁵ <u>100079</u> | Nilus, will be at ICAAC00 |
| ⁴⁶ <u>100027</u> | Pendland |
| ⁴⁷ <u>100048</u> | |
| ⁴⁸ <u>99001</u> | Appelbaum; partial ICAAC99, ICAAC00 |
| ⁴⁹ <u>100078</u> | Ramer |
| ⁵⁰ <u>99014</u> | Dubois |
| ⁵¹ | Scientifically accepted; provide literature references |
| ⁵² <u>99051</u> | |
| ⁵³ <u>99039</u> | |
| ⁵⁴ <u>99038</u> | |
| ⁵⁵ <u>99042</u> | |
| ⁵⁶ | 99051, 99030, 99038, 99042 |
| ⁵⁷ <u>99049</u> | Zhong mechanism of action reference |
| ⁵⁸ <u>99071</u> | Mankin |
| ⁵⁹ <u>99049</u> | |
| ⁶⁰ <u>99038</u> | Shorridge |
| ⁶¹ <u>99040</u> | |
| ⁶² <u>99038</u> | |
| ⁶³ <u>99038</u> | Multiple in-vitro studies |
| ⁶⁴ <u>99051</u> | |
| ⁶⁵ <u>99039</u> | |
| ⁶⁶ | 99058, 100027, 100079 |

general frequency of between 1×10^{-4} to 10^{-67} .

ERADOMYCIN has been shown to be active against most strains of the following microorganisms both *in-vitro* and in clinical infections as described in the INDICATIONS AND USAGE section:

Aerobic Gram-Positive Microorganisms

Staphylococcus aureus (methicillin-susceptible strains; macrolide inducibly resistant and efflux strains)

Staphylococcus epidermidis (methicillin-susceptible strains)

Streptococcus pneumoniae (including penicillin-susceptible, intermediate and resistant strains; macrolide susceptible, intermediate and resistant strains; quinolone susceptible, intermediate and resistant strains)

Streptococcus pyogenes including macrolide susceptible, intermediate and resistant strains;

Aerobic Gram-Negative Microorganisms

Haemophilus influenzae (including beta-lactamase producing strains and beta-lactamase negative ampicillin resistant (BLNAR) strains)

Haemophilus parainfluenzae (including beta-lactamase producing strains)

Moraxella catarrhalis (including beta-lactamase producing strains)

Other Microorganisms

Mycoplasma pneumoniae

Chlamydia pneumoniae (TWAR)

Legionella pneumophila

The following *in vitro* data are available, but their clinical significance is unknown.

Eradomycin exhibits *in-vitro* minimum inhibitory concentrations (MICs) of ≤ 2 $\mu\text{g/ml}$ against most ($\geq 90\%$) strains of the following bacteria; however, the safety and effectiveness of eradomycin in treating clinical infections due to these bacteria have not been established in adequate and well-controlled clinical trials.

Aerobic Gram-positive Microorganisms

Streptococcus agalactiae

Streptococci (Groups C, F, G)

Coagulase negative staphylococci (methicillin susceptible)

Viridans group streptococci

Corynebacterium jeikeium

Corynebacterium spp.

Listeria monocytogenes

⁶⁷

29068, 160027, 100079

Aerobic Gram-negative Microorganisms

Bordetella pertussis

Legionella pneumophila

Neisseria meningitidis

Neisseria gonorrhoeae (including penicillin resistant and quinolone resistant strains)

Anaerobic Gram-positive Microorganisms

Peptostreptococci

Propionibacterium acnes

Clostridium difficile

Clostridium perfringens

Anaerobic Gram-negative Microorganisms

Bacteriodes spp.

Porphyromonas spp.

Prevotella spp.

Dilution Techniques

Quantitative methods that are used to determine minimum inhibitory concentrations (MICs) provide reproducible estimates of the susceptibility of bacteria to antimicrobial compounds. The MICs should be determined using a standardized procedure. Standardized procedures are based on dilution methods (broth or agar) or equivalent with standardized inoculum concentrations and standardized concentrations of erandomycin powder. The MIC values obtained should be interpreted according to the following criteria:

For testing non-fastidious aerobic organisms

| MIC (µg/mL) | Interpretation |
|-------------|------------------|
| <2.0 | Susceptible (S) |
| 4.0 | Intermediate (I) |
| >8.0 | Resistant (R) |

For testing Haemophilus spp.^a

| MIC (µg/mL) | Interpretation |
|-------------|------------------|
| ≤4.0 | Susceptible (S) |
| 8.0 | Intermediate (I) |
| ≥16.0 | Resistant (R) |

^a This interpretive standard is applicable only to broth microdilution susceptibility tests with *Haemophilus* spp. using *Haemophilus* Test Medium (ITM).¹

For testing Streptococcus spp. including Streptococcus pneumoniae^b

| MIC (mcg/mL) | Interpretation |
|--------------|----------------|
|--------------|----------------|

| | |
|------|------------------|
| ≤0.5 | Susceptible (S) |
| 1.0 | Intermediate (I) |
| ≥2.0 | Resistant (R) |

^b These interpretive standards are applicable only to broth microdilution susceptibility tests using cation-adjusted Mueller-Hinton broth with 2-5% lysed horse blood.¹

A report of "Susceptible" indicates that the pathogen is likely to be inhibited if the antimicrobial compound in the blood reaches the concentration usually achievable. A report of "Intermediate" indicates that the result should be considered equivocal, and, if the microorganism is not fully susceptible to alternative, clinically feasible drugs, the test should be repeated. This category implies possible clinical applicability in body sites where the drug is physiologically concentrated or in situations where high dosage of drug can be used. This category also provides a buffer zone that prevents small, uncontrolled technical factors from causing major discrepancies in interpretation. A report of "Resistant" indicates that the pathogen is not likely to be inhibited if the antimicrobial compound in the blood reaches the concentration usually achievable and that other therapy should be selected.

Standardized susceptibility test procedures require the use of laboratory control bacterial strains to control the technical aspects of the laboratory procedures. Standard eradomycin powder should provide the following MICs with these quality control strains:

| Microorganisms | MIC Ranges ⁶⁸ (µg/mL): |
|---------------------------------------------------------|-----------------------------------|
| <i>Staphylococcus aureus</i> ATCC 29213 | 0.016-0.12 |
| <i>Haemophilus influenzae</i> ^c ATCC 49247 | 1.0-4.0 |
| <i>Streptococcus pneumoniae</i> ^d ATCC 49619 | 0.002-0.016 |

^c This quality control range is applicable to only *H. influenzae* ATCC 49247 tested by a microdilution procedure using ITTM.¹

^d This quality control range is applicable to only *S. pneumoniae* ATCC 49619 tested by a microdilution procedure using cation-adjusted Mueller-Hinton broth with 2-5% lysed horse blood.¹

Diffusion Techniques

Quantitative methods that require measurement of zone diameters of growth inhibition provide reproducible estimates of the susceptibility of bacteria to antimicrobial compounds. One such standardized procedure² requires the use of standardized inoculum concentrations. This procedure uses paper disks impregnated with eradomycin (equivalent to 15-mcg eradomycin) to test the susceptibility of bacteria to eradomycin. Interpretation involves correlation of the diameter obtained in the disk test with the MIC for eradomycin.

Reports from the laboratory providing results of the standard single-disk susceptibility test with a eradomycin disk (equivalent to 15-mcg eradomycin) should be interpreted according to the following criteria.

For testing non-fastidious aerobic bacteria:

| Zone Diameter (mm) | Interpretation |
|--------------------|------------------|
| ≥23 | Susceptible (S) |
| 20-22 | Intermediate (I) |
| ≤19 | Resistant (R) |

For testing *Haemophilus spp.*⁶⁹:

| Zone Diameter (mm) | Interpretation ^f |
|--------------------|-----------------------------|
|--------------------|-----------------------------|

⁶⁸ ~~2011~~

NCCLS will also have impact

| | |
|-------|------------------|
| ≥16 | Susceptible (S) |
| 13-15 | Intermediate (I) |
| ≤12 | Resistant (R) |

^a This zone diameter standard is applicable only to tests with *Haemophilus* spp. using HTM.²

For testing *Streptococcus* spp. including *Streptococcus pneumoniae* ^d:

| Zone Diameter (mm) | Interpretation ^f |
|--------------------|-----------------------------|
| ≥20 | Susceptible (S) |
| 17-19 | Intermediate (I) |
| ≤16 | Resistant (R) |

^d These zone diameter standards only apply to tests performed using Mueller-Hinton agar supplemented with 5% sheep blood incubated in 5% CO₂.²

Interpretation should be as stated above for results using dilution techniques. Interpretation involves correlation of the diameter obtained in the disk test with the MIC for eradomycin.

Measurement of MIC or MBC and achieved antimicrobial compound concentrations may be appropriate to guide therapy in some infections. (See **CLINICAL PHARMACOLOGY** section for further information on drug concentrations achieved in infected body sites and other pharmacokinetic properties of this antimicrobial drug product)

As with standardized dilution techniques, diffusion methods require the use of laboratory control microorganisms that are used to control the technical aspects of the laboratory procedures. For the diffusion technique, the eradomycin equivalent to a 15-mcg eradomycin disk should provide the following zone diameters in these laboratory quality control strains:

Zone Diameter Ranges

Staphylococcus aureus ATCC 25923 XXXXXmm

Haemophilus influenzae^b ATCC 49247 XXXXXmm

Streptococcus pneumoniae^c ATCC 49619 XXXXXmm

^b This quality control limit applies to tests conducted with *Haemophilus influenzae* ATCC 49247 using HTM.²

^c This quality control range is applicable only to tests performed by disk diffusion using Mueller-Hinton agar supplemented with 5% defibrinated sheep blood.²

Summaries of susceptibility interpretive criteria and acceptable quality control ranges for eradomycin to be used for validation of susceptibility test results can be shown in the following tables:

Susceptibility Interpretive Criteria for Eradomycin

| Microorganisms | MIC (µg/mL) | | | Disk Diffusion (mm) | | |
|----------------------------------------------------------|-------------|---|-----|---------------------|-------|-----|
| | S | I | R | S | I | R |
| Aerobic Non-Fastidious | ≤2 | 4 | ≥8 | ≥23 | 20-22 | ≤19 |
| <i>Haemophilus</i> spp. | ≤4 | 8 | ≥16 | ≥16 | 13-15 | ≤12 |
| <i>Streptococcus</i> spp. including <i>S. pneumoniae</i> | ≤0.5 | 1 | ≥2 | ≥20 | 17-19 | ≤16 |

S = susceptible, I = intermediate, R = resistant

Acceptable Quality Control Ranges for Eradomycin To Be Used In Validation of Susceptibility Test Results

| Quality Control Strain | MIC (mcg/ml.) | Disk Diffusion (mm) |
|-----------------------------------------------|----------------|---------------------|
| <i>Streptococcus pneumoniae</i> ATCC 49619 | 0.002-0.016 | XXXXXX |
| <i>Haemophilus influenzae</i> ATCC 49247 | 0.03-0.12 | XXXXXXX |
| <i>Staphylococcus aureus</i> ATCC 25913 | 0.016-0.12 | Not Applicable |
| <i>Staphylococcus aureus</i> ATCC 25923 | Not Applicable | XXXXXX |

INDICATIONS AND USAGE

ERADOMYCIN Filmtab tablets are indicated for the treatment of mild to moderate infections caused by susceptible strains of the designated microorganisms in the conditions listed below:

Adults:

Pharyngitis/Tonsillitis due to *Streptococcus pyogenes* (The usual drug of choice in the treatment and prevention of streptococcal infections and the prophylaxis of rheumatic fever is penicillin administered by either the intramuscular or the oral route. ERADOMYCIN is generally effective in the eradication of *S. pyogenes* from the nasopharynx; however, data establishing the efficacy of ERADOMYCIN in the subsequent prevention of rheumatic fever are not available at present.)

Acute maxillary sinusitis due to *Haemophilus influenzae*, *Moraxella catarrhalis*, or *Streptococcus pneumoniae*

Acute bacterial exacerbation of chronic bronchitis due to *Haemophilus influenzae*, *Moraxella catarrhalis*, *Haemophilus parainfluenzae* or *Streptococcus pneumoniae*

Pneumonia due to *Mycoplasma pneumoniae*, *Streptococcus pneumoniae*, or *Chlamydia pneumoniae* (TWAR)

In patients who fail therapy, susceptibility testing should be done if possible. If resistance is demonstrated, alternative therapy is recommended. (For information on development of resistance see **Microbiology** section.)

CONTRAINDICATIONS

ERADOMYCIN is contraindicated for patients with a known hypersensitivity to ERADOMYCIN or any macrolide or ketolide antibiotics.

WARNINGS

ERADOMYCIN SHOULD NOT BE USED IN PREGNANT WOMEN EXCEPT IN CLINICAL CIRCUMSTANCES WHERE NO ALTERNATIVE THERAPY IS APPROPRIATE. IF PREGNANCY OCCURS WHILE TAKING THIS DRUG, THE PATIENT SHOULD BE APPRISED OF ^{69 70 71}. (See PRECAUTIONS - Pregnancy.)

Pseudomembranous colitis has been reported with nearly all antibacterial agents, including ERADOMYCIN, and may range in severity from mild to life threatening. Therefore, it is important to consider this diagnosis in patients who present with diarrhea subsequent to the administration of antibacterial agents.

⁶⁹ See 1

⁷⁰ See 2

⁷¹ See 3

Treatment with antibacterial agents alters the normal flora of the colon and may permit overgrowth of clostridia. Studies indicate that a toxin produced by *Clostridium difficile* is a primary cause of "antibiotic-associated colitis".

After the diagnosis of pseudomembranous colitis has been established, therapeutic measures should be initiated. Mild cases of pseudomembranous colitis usually respond to discontinuation of the drug alone. In moderate to severe cases, consideration should be given to management with fluids and electrolytes, protein supplementation, and treatment with an antibacterial drug clinically effective against *Clostridium difficile* colitis.

PRECAUTIONS

General:

ERADOMYCIN is principally excreted via the liver. ERADOMYCIN may be administered without dosage adjustment to patients with hepatic impairment⁷² and normal renal function⁷³. However, in the presence of severe renal impairment with or without coexisting hepatic impairment, decreased dosage or prolonged dosing intervals may be appropriate.

Information to Patients: ERADOMYCIN tablets can be taken with or without food⁷⁴.

Drug Interactions:

To be written pending outcome of drug interaction studies.

Planned drug interaction studies:

- 1) Ketoconazole⁷⁵
- 2) Impact of rifampin on 773⁷⁶
- 3) Impact of 773 on oral contraceptives⁷⁷
- 4) Impact of 773 on theophylline⁷⁸
- 5) Digoxin⁷⁹
- 6) Impact of 773 on midazolam⁸⁰
- 7) Nifedipine⁸¹
- 8) Statin⁸²
- 9) Warfarin⁸³
- 10) Carbamazepine⁸⁴
- 11) Cyclosporin⁸⁵
- 12) Loratadine⁸⁶

Potentially add general CYP3A statements rather than individually doing studies on individual drugs

Mutagenesis, Carcinogenesis, Impairment of Fertility:

| | |
|-----------------------|-------------------------------------------------------------------------------------------|
| ⁷² M99-125 | Hepatic study |
| ⁷³ M00-111 | Renal study |
| ⁷⁴ M00-AAA | Final biostudy |
| ⁷⁵ 100091 | |
| ⁷⁶ 100092 | M00-156 |
| ⁷⁷ 100100 | M99-128 |
| ⁷⁸ 100101 | M99-139 |
| ⁷⁹ 100102 | |
| ⁸⁰ 100089 | M00-155; If does not increase midazolam conc (not likely), no need to do 100103 or 100104 |
| ⁸¹ 100103 | Pending |
| ⁸² 100104 | Pending |
| ⁸³ 100105 | |
| ⁸⁴ 100107 | |
| ⁸⁵ 100108 | |
| ⁸⁶ 100109 | |

The following *in vitro* mutagenicity tests have been conducted with ERADOMYCIN:

In Vitro Cytogenetics Assay in Human Lymphocytes⁸⁷
 Mouse Lymphoma Assay⁸⁸
 Mouse Micronucleus Test⁸⁹
 Bacterial Reverse-Mutation Test (Ames Test)⁹⁰.

All tests had negative results.

Fertility and reproductive studies have shown that daily doses of up to ? mg/kg/day (X times the recommended maximum human dose based on mg/m²) to male and female rats caused no adverse effects on the estrous cycle, fertility, parturition, or number and viability of offspring. Plasma levels in rats after ? mg/kg/day were X times the human serum levels.⁹¹⁻⁹³

In rabbits, no treatment-related effects on fetal viability or growth were observed.⁹⁴

Long-term studies in animals have not been performed to evaluate the carcinogenic potential of ERADOMYCIN.

Pregnancy: Category B or C⁹⁵.

X number teratogenicity studies in rats (three with oral doses and one with intravenous doses up to X mg/kg/day administered during the period of major organogenesis) and two in rabbits at oral doses up to X mg/kg/day (approximately X times the recommended maximum human dose based on mg/m²) or intravenous doses of X mg/kg/day administered during gestation days X to X failed to demonstrate any teratogenicity from ERADOMYCIN. Two additional oral studies in a different rat strain at similar doses and similar conditions demonstrated a low incidence of cardiovascular anomalies at doses of X mg/kg/day administered during gestation days X to X. Plasma levels after X mg/kg/day were X times the human serum levels. Four studies in mice revealed a variable incidence of cleft palate following oral doses of X mg/kg/day (X and X times the recommended maximum human dose based on mg/m², respectively) during gestation days X to X. Cleft palate was also seen at X mg/kg/day. The X mg/kg/day exposure resulted in plasma levels X times the human serum levels. In monkeys, an oral dose X mg/kg/day (an approximate equidose of the recommended maximum human dose based on mg/m²) produced fetal growth retardation at plasma levels that were X times the human serum levels.

There are no adequate and well-controlled studies in pregnant women. ERADOMYCIN should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus. (See **WARNINGS**.)

Nursing Mothers⁹⁶:

It is not known whether ERADOMYCIN is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when ERADOMYCIN is administered to a nursing woman. It is known that ERADOMYCIN is excreted in the milk of lactating animals and that other drugs of this class are excreted in human milk. Preweaned rats, exposed indirectly via consumption of milk from dams treated with 150 mg/kg/day for 3 weeks, were not adversely affected, despite data indicating higher drug levels in milk than in plasma.

⁸⁷ 100111

⁸⁸ 100114

⁸⁹ 100116

⁹⁰ 100117

⁹¹ 100118 Seg 1

⁹² 100120 Seg 2 (rats)

⁹³ 100119 Seg 3

⁹⁴ 100106

⁹⁵ 100119 Seg 3

⁹⁶ 100110 Study TBD

Pediatric Use:

The safety and effectiveness of ERADOMYCIN in pediatric patients have not been established [If use of the drug in premature or neonatal infants, or other pediatric subgroups, is associated with a specific hazard, the hazard shall be described in this subsection of the labeling, or, if appropriate, the hazard shall be stated in the "Contraindications" or "Warnings" section of the labeling and this subsection shall refer to it.]

***Geriatric Use*⁹⁷:**

In a steady-state study in which healthy elderly subjects (age 65 to 81 years old) were given 150 mg every 24 hours, the maximum serum concentrations and area under the curves of ERADOMYCIN were increased compared to those achieved in healthy young adults. These changes in pharmacokinetics parallel known age-related decreases in renal function. In clinical trials, elderly patients did not have an increased incidence of adverse events when compared to younger patients. Dosage adjustment should be considered in elderly patients with severe renal impairment.

[If clinical studies did not include sufficient numbers (100) of subjects aged 65 and over to determine whether elderly subjects respond differently from younger subjects, and other reported clinical experience has not identified such differences, the "Geriatric use" subsection of PRECAUTIONS shall include the following statement:

"Clinical studies of (name of drug) did not include sufficient numbers of subjects aged 65 and over to determine whether they respond differently from younger subjects. Other reported clinical experience has not identified differences in responses between the elderly and younger patients. In general, dose selection for an elderly patient should be cautious, usually starting at the low end of the dosing range, reflecting the greater frequency of decreased hepatic, renal, or cardiac function, and of concomitant disease or other drug therapy."]

ADVERSE REACTIONS

The majority of side effects observed in clinical trials were of a mild and transient nature.

The most frequently reported events in adults were diarrhea (X%), nausea (X%), abnormal taste (X%), dyspepsia (X%), abdominal pain/discomfort (X%), and headache (X%)⁹⁸. Most of these events were described as mild or moderate in severity. Of the reported adverse events, only X% was described as severe.

In sinusitis studies conducted in adults comparing ERADOMYCIN to amoxicillin/clavulanic acid, there were fewer adverse events involving the digestive system in ERADOMYCIN-treated patients compared to amox/clav-treated patients (X% vs X%; p<0.01). Twenty percent of amoxicillin/clavulanic acid-treated patients discontinued therapy due to adverse events compared to 4% of ERADOMYCIN treated patients.

Taste/GI comparable to Zithromax in AECB study?

*Changes in Laboratory Values*⁹⁹: Changes in laboratory values with possible clinical significance were as follows:

Hepatic - elevated SGPT (ALT) < X%; SGOT (AST) < X%; GGT < X%; alkaline phosphatase < X%; LDH < X%; total bilirubin < X%

Hematologic - decreased WBC < X%; elevated prothrombin time X%

Renal - elevated BUN X%; elevated serum creatinine < X%

GGT, alkaline phosphatase, and prothrombin time data are from adult studies only.

DOSAGE AND ADMINISTRATION

ERADOMYCIN[®] Filmtab[®] (ERADOMYCIN tablets may be given with or without food¹⁰⁰).

⁹⁷ M97-AAA

Study in elderly: need final dosage form/dose

⁹⁸

Phase III studies

⁹⁹

¹⁰⁰ 100064

M97-716

Error! Bookmark not defined.ADULT DOSAGE GUIDELINES

| Infection | Dosage (q24h) | Normal Duration (days) |
|---------------------------------------------------------------------------------------------------------|--------------------------|-----------------------------------|
| Pharyngitis/Tonsillitis | 150 mg | 5 days |
| Acute bacterial sinusitis | 150 mg | 10 days |
| Acute exacerbation of chronic bronchitis: | 150 mg | 5 days |
| Community-acquired pneumonia including <i>mycoplasma</i> , <i>chlamydia</i> and <i>legionella</i> | 150 mg | 7-10 days |

ERADOMYCIN may be administered without dosage adjustment in the presence of hepatic impairment if there is normal renal function^{101, 102}.

HOW SUPPLIED

ERADOMYCIN® Filmtab® (ERADOMYCIN tablets) are supplied as COLOR oval film-coated tablets containing 150 mg of ERADOMYCIN imprinted (on one side) in COLOR with the Abbott logo and a two-letter Abbo-Code designation, DK, in the following packaging sizes:

Bottles of 30 (NDC XXXX-XXXX-XX), ABBO-PAC unit dose strip packages of 100 (NDC XXXX-XXXX-XX), and RAD-PAK™ unit-of-use compliance package of 5 tablets in individual blisters.

CLINICAL STUDIES**Indication XXX**

In a controlled clinical study of XXX performed in the United States, where significant rates of both penicillin-resistant and macrolide-resistant *Strep. pneumoniae* were observed, ERADOMYCIN was compared to XXX. In this study, very strict evaluability criteria were used to determine clinical response. For the XXX patients who were evaluated for clinical efficacy, the clinical success rate (i.e., cure plus improvement) at the post-therapy visit was XX% for ERADOMYCIN and XX% for the XXX.

In a smaller number of patients, microbiologic determinations were made at the pre-treatment visit. The following presumptive bacterial eradication/clinical cure outcomes (i.e., clinical success) were obtained:

¹⁰¹ [160070](#) Hepatic study (M99-126)
¹⁰² [160071](#) Renal study (TBD)

Error! Bookmark not defined.U.S. Acute XXX Study
ERADOMYCIN vs. Comparator XXX

| EFFICACY RESULTS | |
|-------------------------|-----------------------------------------------------|
| PATHOGEN | OUTCOME |
| <i>S. pneumoniae</i> | ERADOMYCIN success rate, X/X (X%) control X/X (X%) |
| <i>H. influenzae*</i> | ERADOMYCIN success rate, X/X (X%), control X/X (X%) |
| <i>M. catarrhalis</i> | ERADOMYCIN success rate, X/X (X%), control X/X (X%) |
| <i>S. pyogenes</i> | ERADOMYCIN success rate, X/X (X%), control X/X (X%) |
| Overall | ERADOMYCIN success rate X/X (X%), control X/X (X%) |

None of the *Strep. pneumoniae* isolated pre-treatment was resistant to ERADOMYCIN; X% were resistant to the control agent.

Safety:

The incidence of adverse events in all patients treated, primarily diarrhea and vomiting, did not differ clinically or statistically for the two agents.

In two other controlled clinical trials of indication XXX performed in the United States, where significant rates of penicillin-resistant and macrolide-resistant *Strep. pneumoniae* were found, ERADOMYCIN was compared to XXX. In these studies, very strict evaluability criteria were used to determine the clinical responses. In the XXX patients who were evaluated for clinical efficacy, the combined clinical success rate (i.e., cure and improvement) at the post-therapy visit was XX% for both ERADOMYCIN and the control.

For the patients who had microbiologic determinations at the pre-treatment visit, the following presumptive bacterial eradication/clinical cure outcomes (i.e., clinical success) were obtained:

Error! Bookmark not defined.Two U.S. Acute XXX Studies
ERADOMYCIN vs.
Comparator XXX

| EFFICACY RESULTS | |
|-------------------------|-----------------------------------------------------|
| PATHOGEN | OUTCOME |
| <i>S. pneumoniae</i> | ERADOMYCIN success rate, X/X (X%), control X/X (X%) |
| <i>H. influenzae*</i> | ERADOMYCIN success rate, X/X (X%), control X/X (X%) |
| <i>M. catarrhalis</i> | ERADOMYCIN success rate, X/X (X%), control X/X (X%) |
| <i>S. pyogenes</i> | ERADOMYCIN success rate, X/X (X%), control X/X (X%) |
| Overall | ERADOMYCIN success rate, X/X (X%), control X/X (X%) |

Of the *Strep. pneumoniae* isolated pre-treatment, X% were resistant to ERADOMYCIN and X% were resistant to the control agent.

Safety:

The incidence of adverse events in all patients treated, primarily diarrhea (X% vs. X%) and XXX (X vs. X%)

PART 3

was clinically and statistically lower in the ERADOMYCIN arm versus the control arm.

ANIMAL PHARMACOLOGY AND TOXICOLOGY

ERADOMYCIN is rapidly and well-absorbed with dose-linear kinetics, low protein binding, and a high volume of distribution. Plasma half-life ranged from 1 to 6 hours and was species dependent. High tissue concentrations were achieved, but negligible accumulation was observed. Fecal clearance predominated. Hepatotoxicity occurred in all species tested (i.e., in rats and monkeys at doses 2 times greater than and in dogs at doses comparable to the maximum human daily dose, based on mg/m^2). Renal tubular degeneration (calculated on a mg/m^2 basis) occurred in rats at doses 2 times, in monkeys at doses 8 times, and in dogs at doses 12 times greater than the maximum human daily dose. Testicular atrophy (on a mg/m^2 basis) occurred in rats at doses 7 times, in dogs at doses 3 times, and in monkeys at doses 8 times greater than the maximum human daily dose. Corneal opacity (on a mg/m^2 basis) occurred in dogs at doses 12 times and in monkeys at doses 8 times greater than the maximum human daily dose. Lymphoid depletion (on a mg/m^2 basis) occurred in dogs at doses 3 times greater than and in monkeys at doses 2 times greater than the maximum human daily dose. These adverse events were absent during clinical trials.

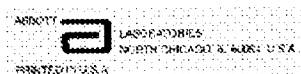
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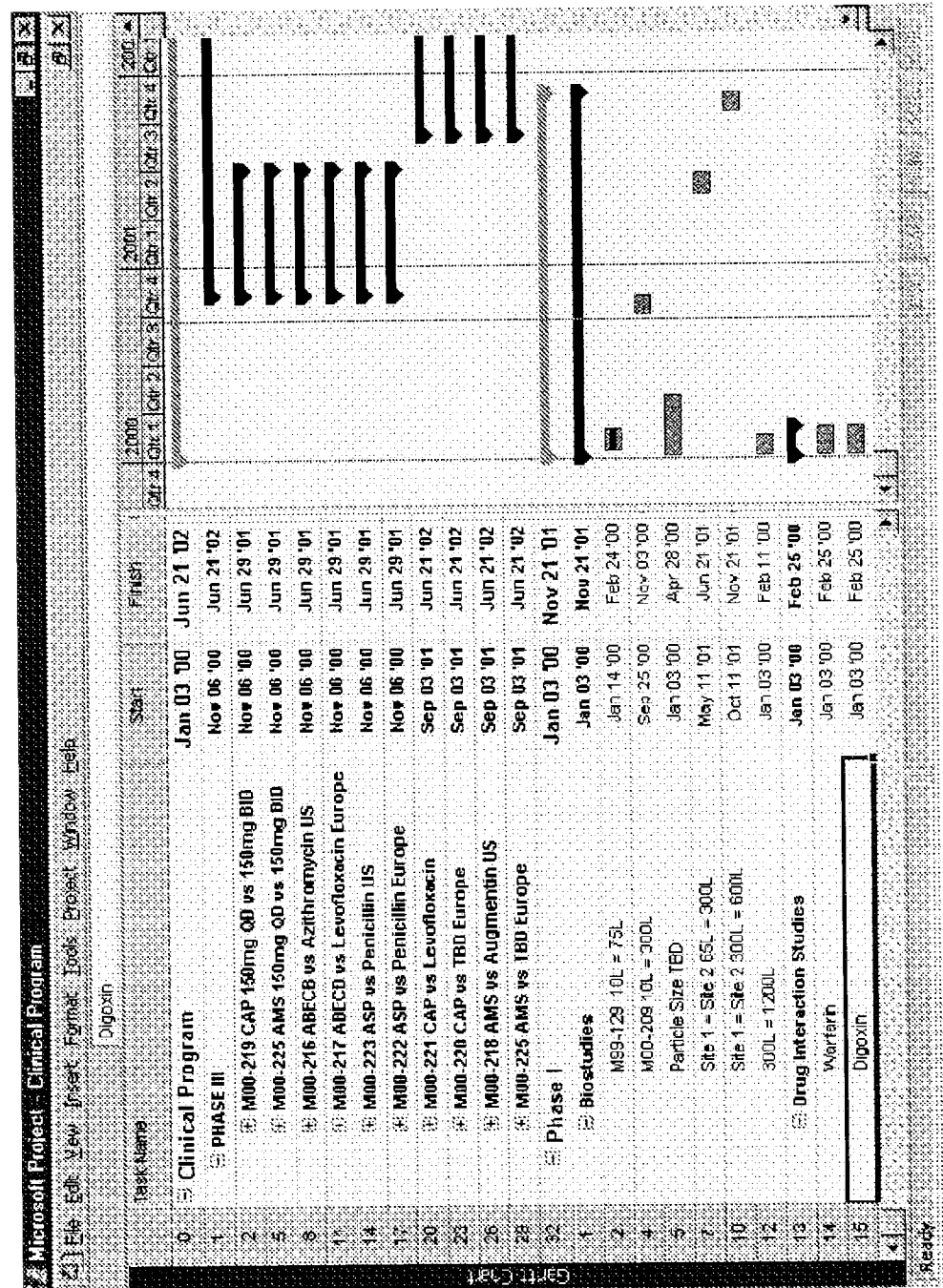
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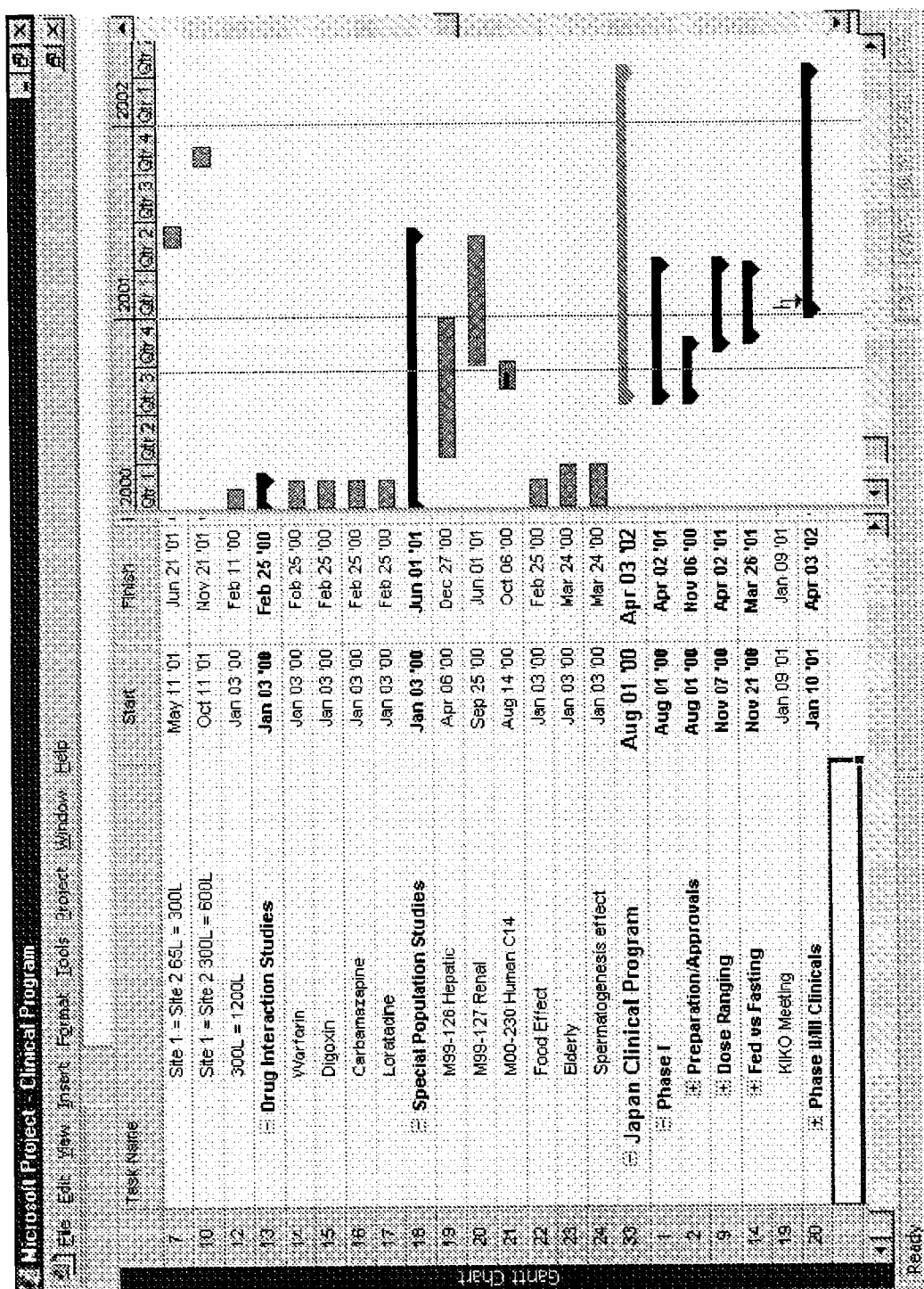
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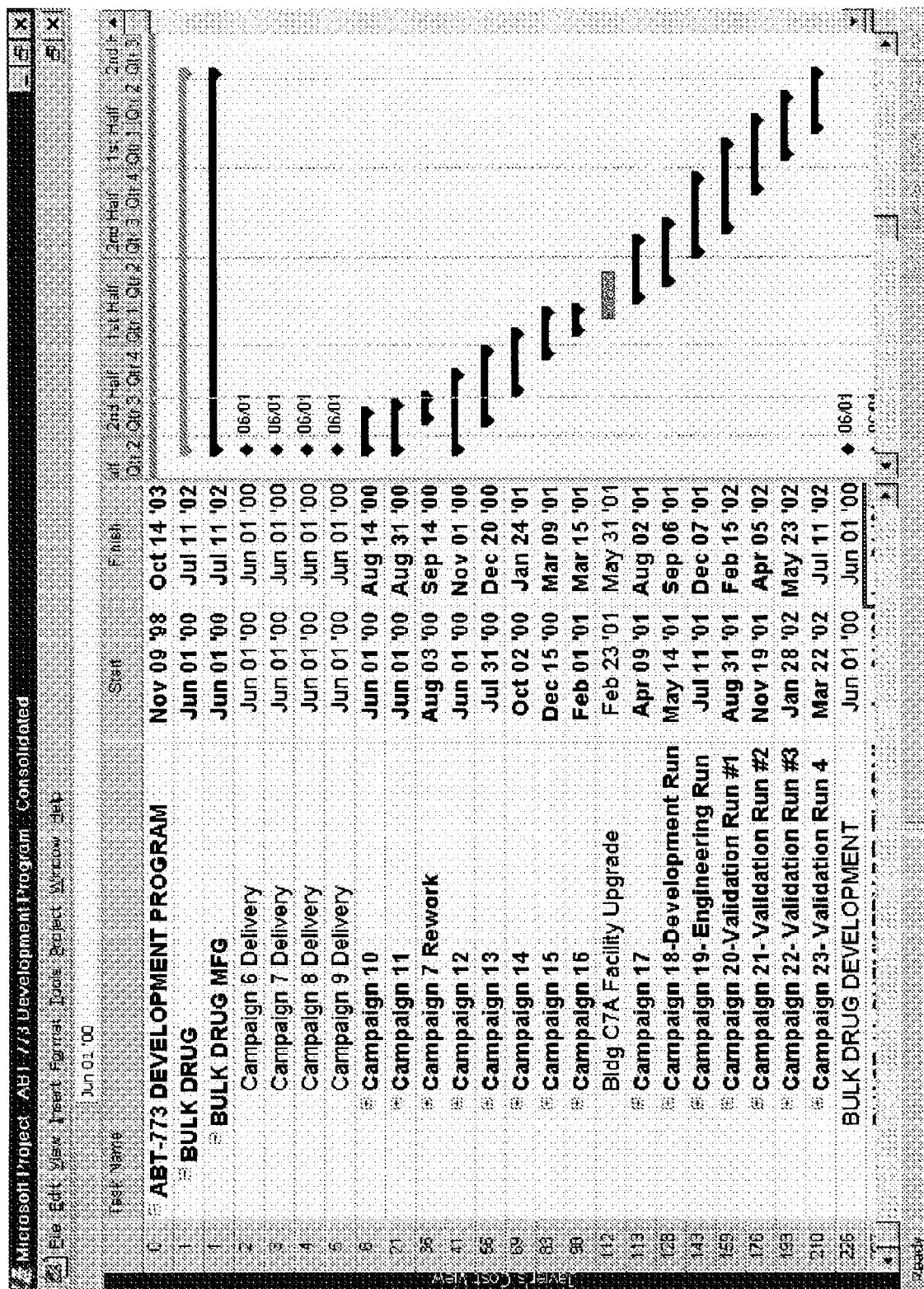
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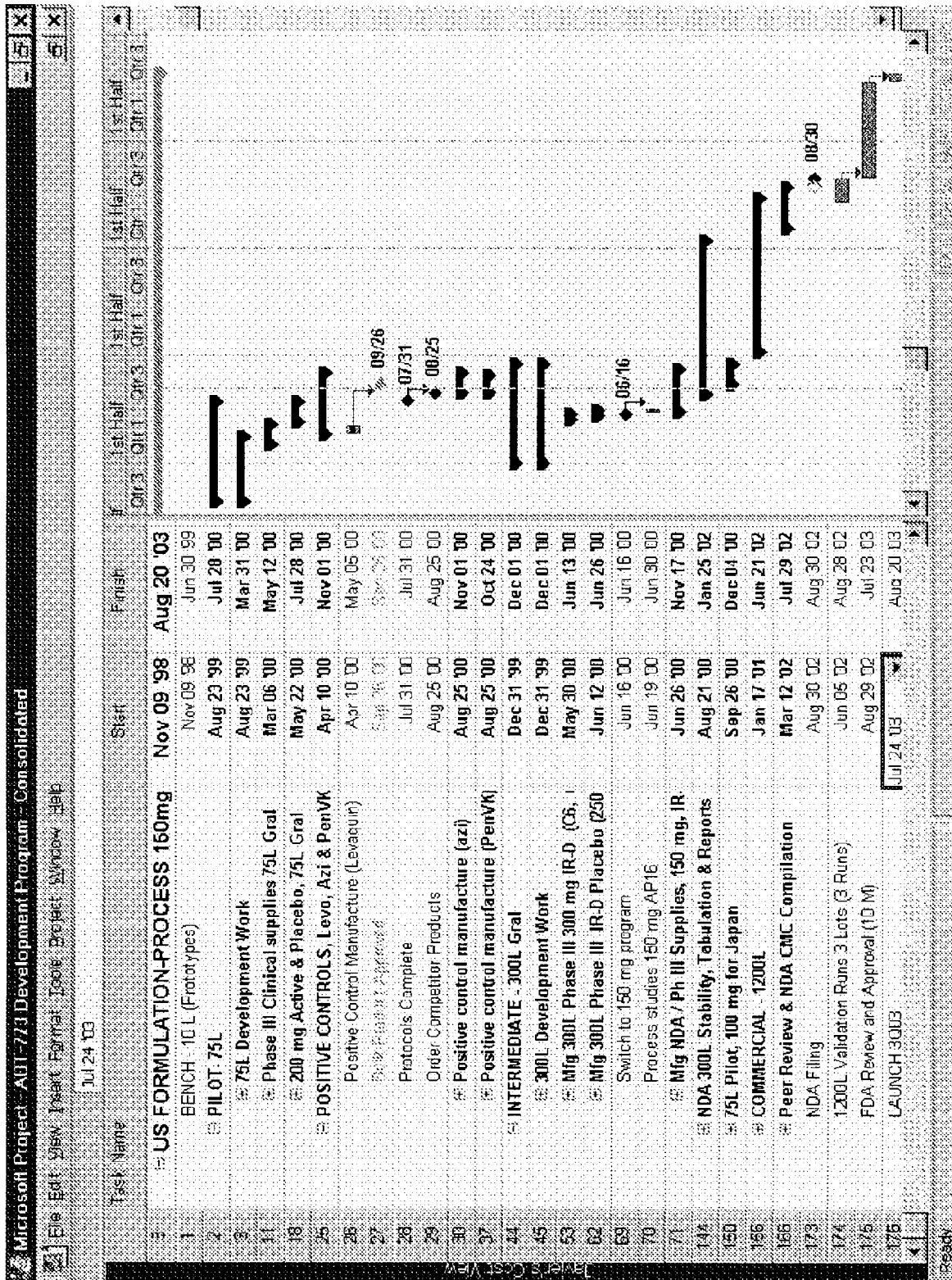
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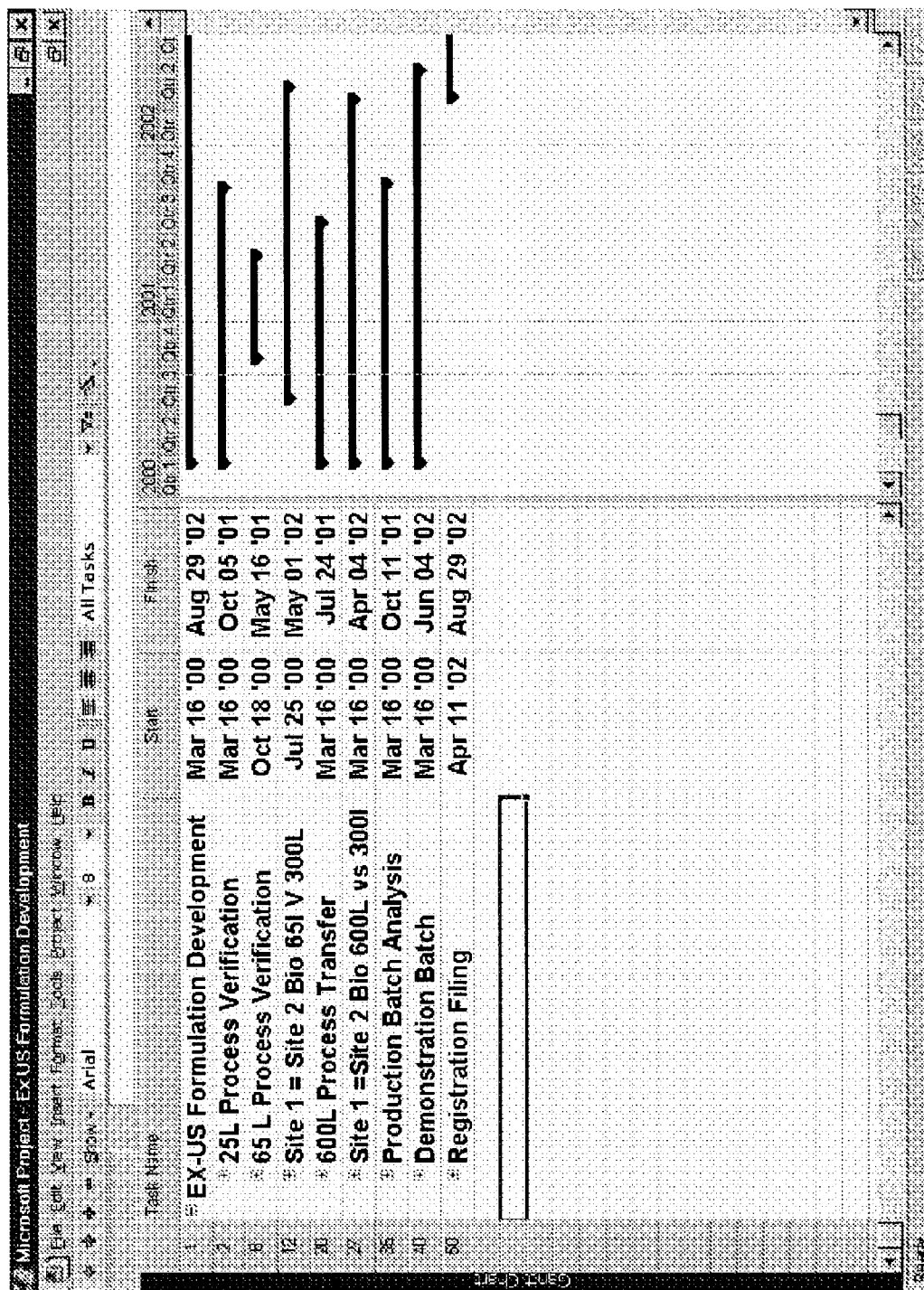


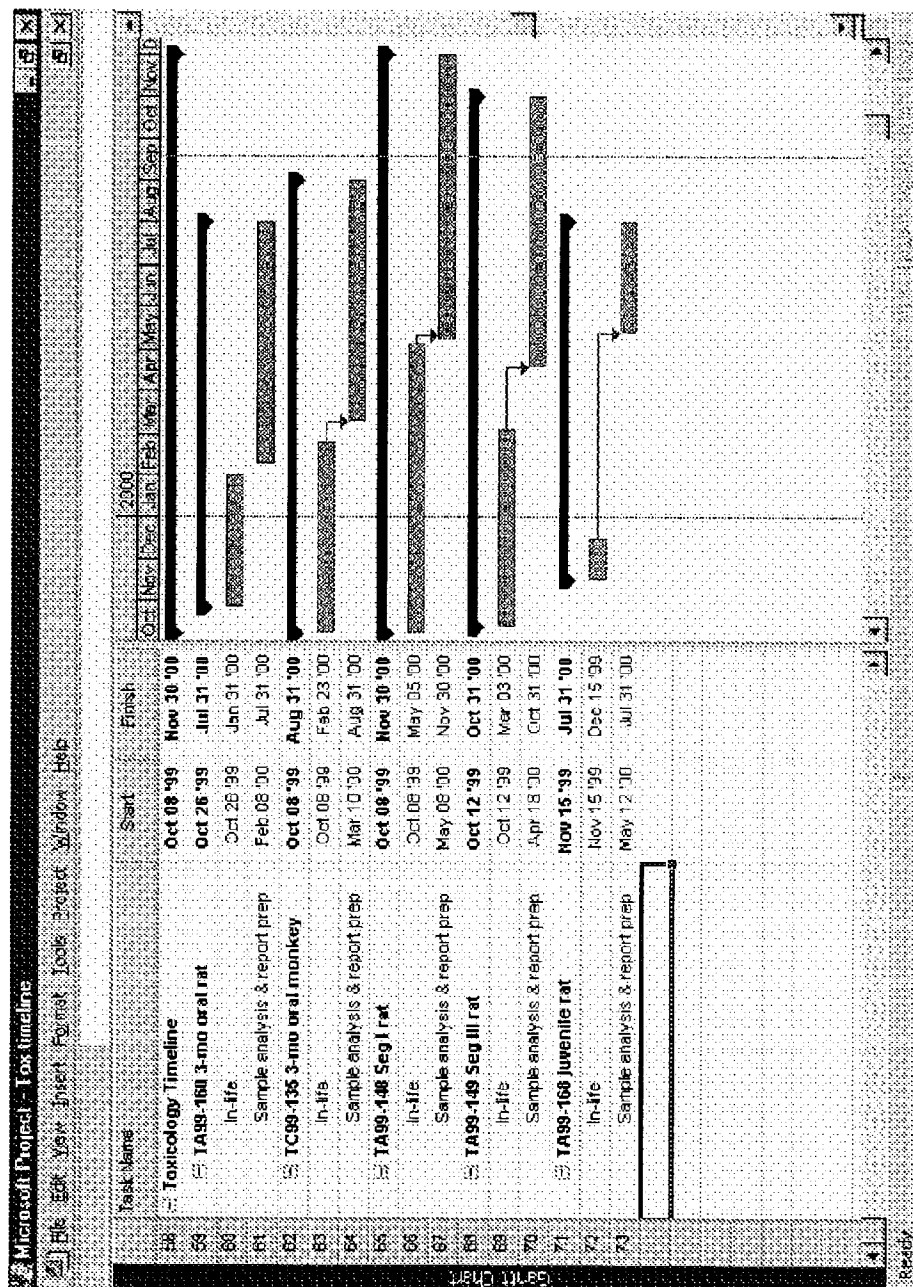












5.0 Project History

5.1 Expert Strategic Review Process - Summaries

5.2 Highlights re: NCE

- ABT-773 was approved by PPCC in 03/97 for development by the Macrolide Venture. Projected NDA date was 12/00.
- Fifty kg of drug was delivered in 1997. Drug chemistry and cost of drug was a major challenge to development cost and timing. NDA projected date was moved to 03/01 with 50% probability.
- First Phase I study was initiated in Netherlands in 11/97. Based on PK results, the request for a QD ER formulation and no major breakthroughs in chemistry, the NDA projected date was moved to 06/02 with 80% probability.
- All process chemistry efforts and delivery activities were put on hold in 04/98 due to concerns of GI/taste issues with the drug. A comparative safety study using 300mg and 600mg/day of ABT-773 vs Clari 500mg bid was initiated. NDA projected date was moved to 09/02 with 80% probability.
- The encouraging safety results lifted the hold on the process chemistry and delivery activities. For 5 months there were no efforts on process research and delivery activities for drug substance. The first ER prototypes were not acceptable. A Phase IIA study using unformulated capsules was initiated in Europe in AECB patients by end of 1998. NDA projected date was kept at 09/02 with 80% probability.
- Significant breakthroughs were achieved in bulk drug synthesis and an ambitious development program was initiated by end of 1998 to develop a QD formulation. Three immediate release and twelve extended release formulations were evaluated with immediate release capsule formulation (IR-A) serving as the reference formulation. After a review of the preliminary data of these studies, an immediate release tablet formulation (IR-C) was chosen on 8/99 for further development based on pharmacokinetics, safety, and ease of manufacture. The Venture had undertaken a challenging chemistry, formulation and clinical development plan and the NDA projected date had been brought forward to 12/01.
- The Phase 2a study indicated that 100 mg TID is an effective dose in AECB in terms of clinical and bacteriological outcomes and has an acceptable safety profile. Based on these results, 300 mg QD was selected as the middle dose for the Phase 2b trials (a preferred regimen over a TID regimen for patient compliance) since the 100 mg TID had demonstrated acceptable efficacy/safety and the QD regimen provided greater exposure than the TID regimen.
- Three Phase 2b studies were started in Sept. 1999 in both the US and EU investigating ABT-773 once daily doses. M99-054 - Community-acquired pneumonia (300 mg or 600 mg once daily for 7 days). M99-053 - Acute bacterial sinusitis (150 mg, 300 mg, or 600 mg once daily for 10 days). M99-048 - Acute bacterial exacerbation of chronic bronchitis (150 mg, 300 mg, or 600 mg once daily for 5 days)
- Scale-up activities to develop a 300mg tablet were initiated at the 75L pilot scale in 9/99, moving to a 300L intermediate scale in Jan 2000. A bioequivalence study was successful comparing the bench scale clinical lots to the 75L pilot scale lots.

- The efficacy (clinical/bacteriology) data from the Phase 2b studies indicated that 150 mg, 300 mg and 600 mg were effective in treating subjects with ABPCB (5 days) and ABS (10 days). The 300 mg and 600 mg were both effective doses to treat CAP (7 days) subjects.
- The safety data indicated that all doses studied did not yield any clinically significant safety abnormalities as far as elevation of liver enzymes or QT prolongation are concerned. The 300 mg and 600 mg doses exhibited moderate amounts of taste disturbance and GI side effects, which were mainly diarrhea, nausea and vomiting.
- Based on the Phase 2b efficacy and safety results, the decision was made to change the tablet dose from 300mg to 150mg. This decision moved the regulatory filing date forward 8 months to Aug 2002 and postponed the start date of the Phase III clinical studies to Nov 2000, in order to prepare 150mg clinical supplies.
- A Japanese bridging study was conducted in Hawaii to evaluate safety and pharmacokinetics of Japanese and non-Japanese subjects. Over the studied doses (150, 300 and 600 mg single and multiple QD), ABT-773 AUC but not Cmax deviated from dose-proportionality in the Japanese and non-Japanese subjects. At equivalent doses, the Japanese subjects had about 50% greater ABT-773 AUC than the non-Japanese subjects. Based on this result, the Japanese Phase I program will be repeated in Japan. Once Phase I results are available and the clinical agency KIKO has been consulted, the Phase II/III program in Japan will be finalized. It is unknown at this time if a separate Japanese dose will be required.

5.1 Historical Changes to ABT-XXX Target Product Profile

| Table 4.0.a Historical Changes to ABT-XXX Target Product Profile | | |
|-------------------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------------------|---------------------------------------------------------|
| PPCC/DDC Profile (12/10/97) | Current Profile (9/00) | Rationale for Profile Change |
| Activity against Gram +, Gram -, atypicals | Activity against Gram +, Gram -, atypicals | No Change |
| Activity against <i>H. influenzae</i> = azi | Activity against <i>H. influenzae</i> = azi | No Change |
| Active against 80% of Gram + resistant strains of efflux and MLS c | Active against 80% of Gram + resistant strains of efflux and MLS c | No Change |
| Active against most macrolide resistant pathogens on a bacterial worldwide-susceptibility panel | Active against most macrolide resistant pathogens on a bacterial worldwide-susceptibility panel | No Change |
| Maintain balanced plasma/tissue levels similar to clari | Maintain balanced plasma/tissue levels similar to clari | No Change |
| Incidence of GI side effects=cephalosporins | Incidence of GI side effects=azi | Azithromycin is a more important competitor in the U.S. |
| Incidence of drug-interactions = clari, no contraindications | Incidence of drug-interactions = clari, no contraindications | No Change |
| QD dosing adult/tablet | QD dosing adult/tablet | No Change |
| QD dosing ped OS | QD dosing ped OS | No Change |
| BID dosing for IV | QD dosing for IV | Current competition is QD |
| Less painful IV at injection site than clari | Comparable pain at injection site than azi | Azi has less pain than clari. |
| Less metallic taste for tablet than clari. | Less metallic taste than clari XL | Clari XL now available. |

| | | |
|----------------------------------------------------------------------------------------------------------|------------------------------------|-----------------------------------------------------------------------------------------------------------------------|
| OS equal in taste to cephalosporins | OS equal in taste to Azi, Omnicef | Azi and Omnicef most important comparators. |
| 5-day therapy for most indications; up to 10 days for serious infections. 3 day therapy for pharyngitis. | 5-day therapy for most indications | No Change |
| Bulk drug cost less than \$2500/kg at launch and \$1250/kg 3 years post launch. | COGS > 80% SMM at launch | No Change |
| Maximum adult dose per day of 1 gram. | | No Change |
| Can be given with or without food. | | Food effect study to be repeated with final formulation, current studies indicate better absorption with food. |

ABT-773 Update February 12, 2001

Introduction

ABT-773 is a ketolide antimicrobial, an evolutionary step from the macrolide antimicrobials such as erythromycin and the new generation macrolides like clarithromycin and azithromycin. It is in phase III development as a replacement to clarithromycin.

The antibiotic market is a large market (\$20.5 Billion in 1999) and is expected to expand on a global sales basis (\$26.5 Billion in 2005). The majority of the markets sales are in the oral tablet/capsule segment. Market sales increases are being driven by replacement of older/cheaper agents with branded agents. Zithromax has driven market demand for cost/convenience/tolerability, while the quinolones (Levaquin, Tequin, Avelox) are the fastest growing segment, playing into resistance concerns. Resistance is a major driving force for both the quinolones and ketolides development.

Ketolides are a Novel Class of Antimicrobial

- Active includes key respiratory tract infection pathogens including macrolide and penicillin resistant *S. pneumoniae* and *S. pyogenes*
- Bactericidal activity
- Prolonged post antibiotic effect
- Reduced resistance development

ABT-773 is the most active ketolide presently under development. It is 5 to 10 times more active than telithromycin (Aventis ketolide) against *S. pneumoniae* and *S. pyogenes* including resistant strains. It has equal activity to telithromycin and azithromycin against *H. influenzae*. The increased activity can be attributed increased ribosomal binding. Compared to macrolides that bind only to domain V, ABT-773 binds to both domains II and V. The binding is essentially irreversible and provides bactericidal activity against *S. pneumoniae*.

Key issues facing the ABT-773 development program are summarized below

QTc Issues

The potential for QTc prolongation is currently a prominent issue facing drug development across therapeutic areas-worldwide. Antimicrobial agents including macrolides and quinolones are of concern to regulatory agencies. There is considerable scientific uncertainty in relating the findings from in vitro assays and animal models to clinical risk of malignant arrhythmias. In an effort to gain more

knowledge these agencies are requiring the pharmaceutical companies to do additional test including

- ICH guidelines require data from animal models and 200 patients
- FDA is in the process of evaluating all drug class known to have a potential for prolonging QTc (erythromycin and clarithromycin)
- FDA has question whether ketolides behave like macrolides
- FDA requested additional dog tox work to evaluate QTc of ABT-773
- ABT-773 studies required including ECG monitoring in pivotal Phase 3 studies.
- FDA may require a Phase I study in patients with underlying cardiac disease, but the design for these studies has not been determined.
- Some antimicrobials now contain warnings for QT prolongation such as moxifloxacin.
- Telithromycin (Ketek) data residing at FDA will be reviewed by FDA Advisory Committee at a meeting scheduled for May 2001 probably related to concerns about efficacy and not related to QTc concerns.

The ketolide ABT-773 will be considered guilty until proven innocent because it is related to erythromycin and clarithromycin which are also suspect and under scrutiny. ABT-773 has the following data related to its potential or lack of potential to affect the QT interval.

- Preclinical data positive for QTc dose response.
- A possible dose effect in Phase I at total daily dose ≥ 800 mg.
- No significant QT effect observed when ABT-773 was administered with the metabolic inhibitor ketoconazole. (Increased ABT-773 Cmax 5X)
- No concentration response in Phase I studies (≤ 300 mg).
- No consistent QT effect observed at clinical doses studied in Phase IIB studies. (150 mg QD to 600 mg QD)

The Venture plan for dealing with the uncertainties related to developing a drug which has an unknown potential for prolonging the QT intervals is to pro-actively attempt to find out as much about our drug and the science related to QTc by;

- Completed preclinical evaluation of ABT-773
- Initiate FDA recommended dog studies.
- Completed ECG monitoring of >200 patients in Phase II and III
- Continue to monitor QTc and electrolytes in Phase III programs.
- Perform FDA requested study of QTc in patients with pre-existing cardiac disease; perform phase I study as required by CPMP.
- IV ABT-773 Phase I study will monitor QTc carefully
- Consult with Drs. Morganroth and Moss QTc advisors.

Liver Toxicity Issues

The FDA has similar concerns regarding the potential for liver toxicity of new drugs as it has for QTc issues, since both of these problems have resulted in

drugs being removed from the market shortly after approval. The concerns have been directed at the quinolones, but all antimicrobials are under going extensive evaluations. The FDA has a meeting on guidance to industry on how to study the potential for liver toxicity, scheduled for February 11-12, 2001. Jean Fox will attend this meeting and report back on it so that we will be able to update this topic at the February meeting.

In the Japanese bridging study run in Hawaii we saw increases in LFTs in Japanese subjects. This was very disturbing, since increases in LFTs were seen only in the Japanese subjects. In addition the Japanese subjects had AUCs which were 50% higher than the western subjects. LFTs in over 1000 western subjects did not show any problems. Since, the Japanese subjects with elevated LFTs did not show a dose response, it was felt that the changes in LFTs might be related to the high caloric diet on the unit. To answer this question Phase I food interaction and a repeat of the bridging study was preformed in Japan. The results of this study showed no evidence of any problem with LFTs in the Japanese or Caucasians. Based on the encouraging results we will continue moving forward with the Japan Program.

Phase III Tablet Program

The Phase III tablet program is underway after several delays related to manufacturing of the 150 mg tablet to replace the 300 mg tablets and the late date (11/27/00) of the FDA End of Phase II meeting. The present plan is to complete the Phase III 150 mg once daily indications in the US and Europe this year. These studies include two pharyngitis studies compared to penicillin 500 mg TID, one ABECB study in the US compared to Azithromycin, and one European ABECB study compared to Levofloxacin. The CAP and sinusitis dose selections studies are running globally, but no European sites are enrolling yet due to the changes in the protocol following the FDA End of Phase II meeting. We are increasing sites and planning to go to the Southern Hemisphere if needed to complete the studies before the start of the fall respiratory season. These changes have added additional costs that will add approximately \$5.0 MM to the budget.

The results of the CAP and Sinusitis studies have the potential of generating divergent development paths based on differences in AI and PPD regulatory and commercial considerations. PPD would prefer to have 150 mg once daily for all indications and AI would prefer 150 mg once daily for pharyngitis and ABECB and 150 mg BID for CAP and sinusitis. Once we complete the study we will need to meet to iron out the possible options.

ABT-773 IV Formulation Program

The IV formulation program is presently unfunded. The IV program is important to overall program because of the following;

- Hospital formulary acceptance
- XX% share gain in Tab sales due to step-down therapy
- Positions 773 for serious infections
- Support for *S. pneumoniae* resistance claim
 - FDA indicated that bacteremic patients will be important to establish body of evidence for this claim
- Provide additional information on QTc effects

The ABT-773 IV program received partial funding last year both from PPD and HPD, but has not been funded for 2001. The following outlines the IV program fund and funding needed.

- PPD/HPD Collaboration initiated 9/99
- PPD funded Program 01/00-08/00 (\$1.4MM)
 - Formulation development (lactate salt, lyophilized powder)
 - Animal pain models
 - Two week Tox study (monkey)
- HPD funded Program 08/00-12/00 (\$0.8MM)
 - Two week Tox study (rat)
 - Clinical supplies for Phase I
 - Stability program
- 2001 funding
 - HPD first pass funding cut for 773 IV (\$7MM)
 - Milestone funding to Phase I Go/No Go (\$1MM)
- Total program development costs 2000 - 2003 (\$22.5MM)

The clinical program with 2001 funding decision in February will included;

- | | |
|--------------------------------------------|---------|
| • Single Dose-rising Phase I study | Apr/01 |
| • Multiple Dose Phase I with selected dose | June/01 |
| • File US IND | Oct/01 |
| • Initiate Phase III | Dec/01 |
| – 2 step-down CAP studies (US/Europe) | |
| – 2-3 days dosing | |
| – Two seasons to complete | |
| • Filing | Aug/03 |

The Venture would recommend funding the Phase I study to determine safety and tolerability profile as a GO/No Go decision. Assuming a GO decision we would need \$7 MM 2001 to start Phase III program.

Pediatric Program

The pediatric suspension program is on hold. ABT-773 is 5 to 7 times more bitter than clarithromycin. This will make the development of an acceptable formulation very difficult. The first prototype tested had a taste that was better than clarithromycin but not as good as azithromycin. The pharmacokinetics showed AUCs that were only 70% of the tablet formulation. Even with the difficulties of making an acceptable formulation the pediatric formulation would have benefits including increasing the perception of safety, better pricing and acceptance in European markets, and FDA requires studies in pediatrics. The Venture would recommend continuing the hold until we resolve other issues and then re-evaluate possible ways of overcoming the taste problem.

Japan Development Program

The Japan development program is planned in coordination with Taisho and Dainabot. Taisho funds 10.69% of global development costs and 50% of local Japan costs. The Venture is attempting to use a bridging strategy as the primary plan for development in Japan. The Phase I studies in Japan which were initiated in response to the LFT problems in the first bridging study, have been completed. There were not increases in the LFTs of the Japanese or Caucasians in the study. We will be meeting with Taisho and Dainabot to formulate a plan to present to Kiko in the 2nd or 3rd Quarter.

PART 4



ABT-773 Update February 12, 2001

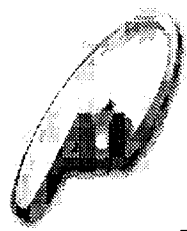
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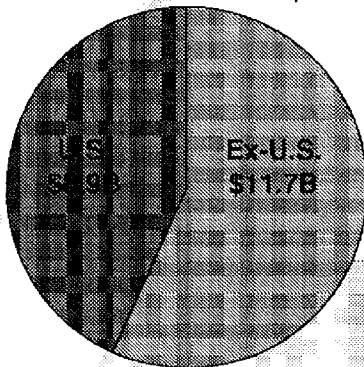
Agenda

- Introduction
- The molecule
- Phase III tablet program Issues
 - QT
 - Liver Function
 - Dosing
- IV program
- Pediatric program
- Japan program

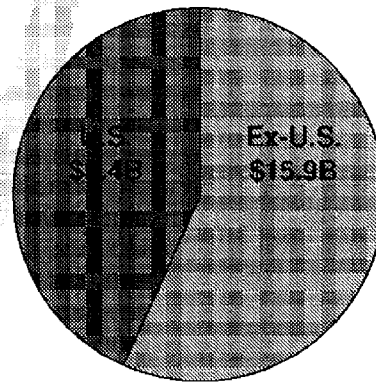


Global Antibiotic Market Sales Current vs Future Projection

1999 Global Sales \$20.6B



2005 Global Sales \$25.3B



The antibiotic market is a large market and is expected to expand on a global sales basis



Global Market Drivers

Negative vs Positive Drivers

- **Antibiotic Resistance**

Increasing sensitivity toward "appropriate use" may have negative impact on usage ↓

Requires new agents to keep ahead of resistant pathogens; substitution of older generic agents with newer branded agents ↑

- **Patent Expirations**

May increase price sensitivity and bargaining power of MCOs ↓

Use of generic agents tend to decrease over time; obsolescence/resistance may further that trend ↑

- **Market expansion ex-US** ↑

- **Unmet Need** ↓

—Overall unmet need relatively low

—Cost, convenience, tolerability take on added importance

—Increasing use of "implied efficacy" metrics i.e. MICs, resistance surveillance, AUC/MIC, MPC, kill kinetics

- **Competition** ↓

—6 NDAs/approvals in last 12 months; Avelox, Tequin, Factive, Spectracel, Ketek, Zyvox

—Continued discovery/development activity by key competitors

—High level of promotional activity

Negative driver ↓

Positive driver ↑

Key Success Factors

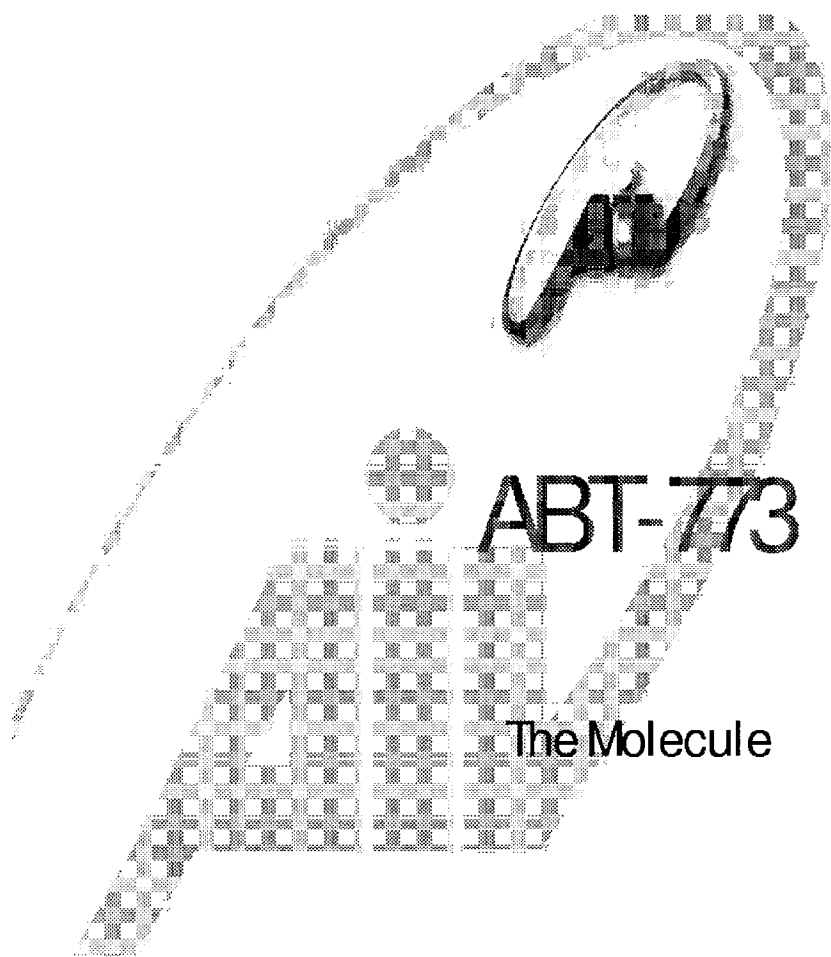
U.S. vs ex-U.S.

| | | U.S. Assessment | Ex-U.S. Assessment |
|---------------|-------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Profile | Efficacy | ++ Requires a certain baseline level of efficacy across all indications as a "ticket to entry", but is difficult to differentiate agents based on efficacy | +++ While also difficult to differentiate based on efficacy, efficacy takes on added importance with respect to regulatory approval, especially in CAP |
| | Tolerability | +++ Success of Zithromax and Levaquin have redefined expectations for tolerability of new agents; agents must offer very good tolerability given numerous alternatives | ++ Although important, markets are willing to bear somewhat higher incidence of adverse events, provided they are not severe (i.e. taste perversion); over time, however, AE hurdles will continue to be increased |
| | Convenience | +++ Zithromax and recent quinolones have moved the market toward short course therapies dosed once daily; Biaxin in 1991 represented the last major BID entrant | ++ While in some cases durations are even shorter (e.g. 3-day AECB), market levies relatively minor penalties for BID dosing |
| | Resistance Claims | ++ Important to leverage the overall ketolid's message, and to maximize regulatory access, although availability of data may be able to accomplish same end | +++ May prove critical in the regulatory decision of approvability, as well as in setting premium pricing |
| | Price | ++ Able to set price in accordance with optimal price/demand relationship; only moderate price sensitivity in market, though this could increase with increased number of generic competitors over mid-term | +++ Pricing figures heavily into the overall profitability of the compound and is governed by merits of product profile relative to other agents |
| Regulatory | Approvability | ++ With data showing equivalence to comparators, is not a major area of concern | +++ Will take into consideration PK profile in addition to clinical data, which could weaken argument for approval; given the pivotal nature of CAP approval to overall compound viability, regulatory risk is magnified; will require very strong clinical data if 150 mg QD is to be supported |
| Profitability | COGS | ++ Allows for ~50% SMM given price parity to Zithromax | ++ Due to pricing constraints, COGS represents a larger issue; current estimates are 76% SMM at launch rising to 87% peak |
| | Price | ++ Assumes price parity to Zithromax | +++ Profile may limit optimal pricing |

+ Minor Factor

++ Moderate Factor

+++ Major Factor



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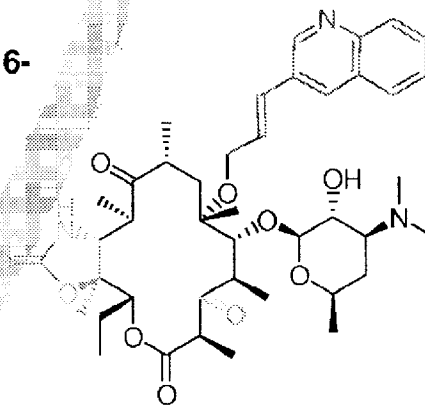
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ABT-773 Ketolide

- Quinolylallyl propenyl moiety at the 6-O-position

- Keto group at the 3-position

- Carbamate group at the 11, 12-position



ABT-773



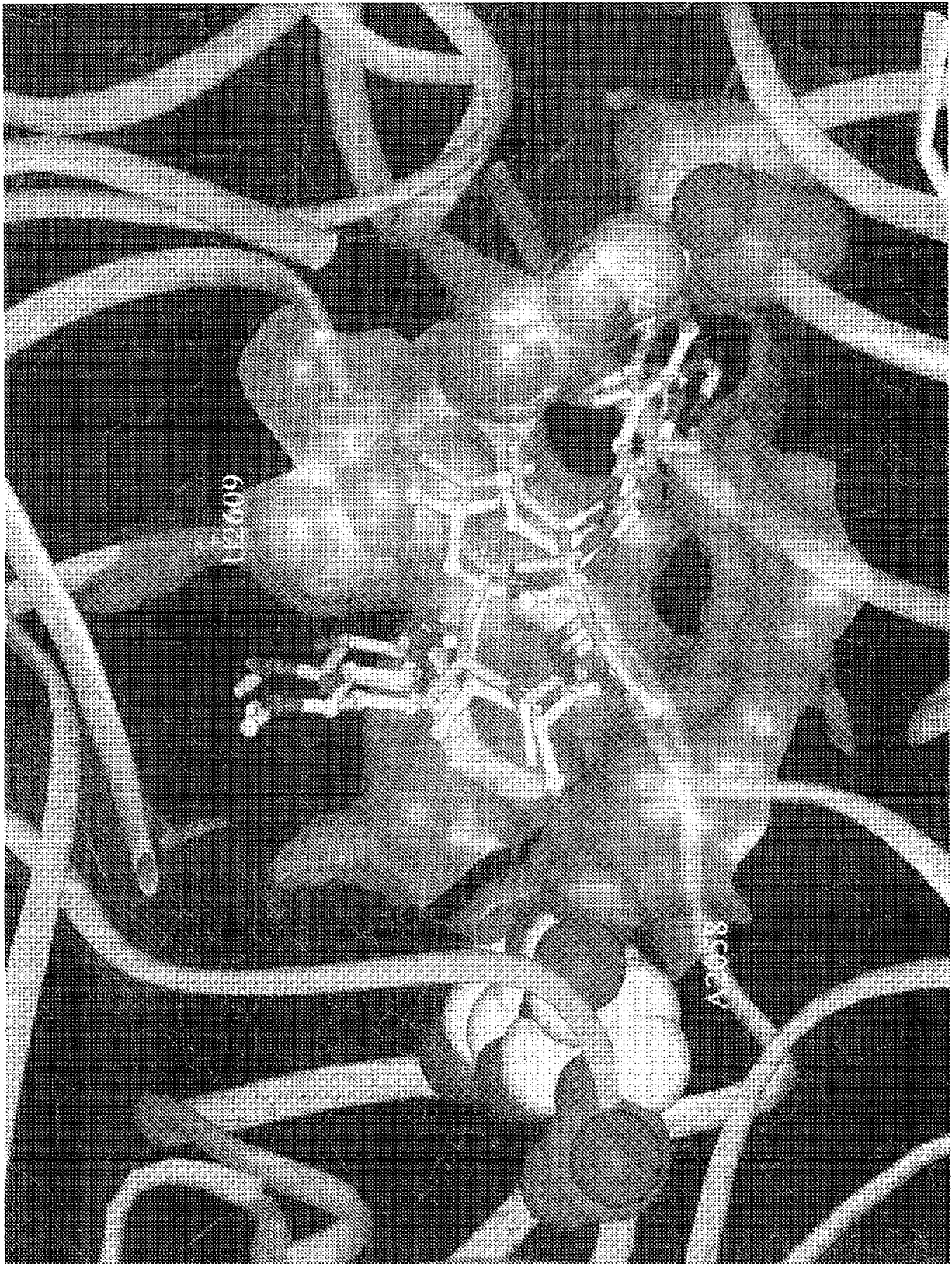
ABT-773 Ketolide

- **Ketolides are a Novel Class of Antimicrobial**

- Active includes key respiratory tract infection pathogens including macrolide and penicillin resistant *S. pneumoniae* and *S. pyogenes*
- Bactericidal activity
- Prolonged post antibiotic effect
- Reduced resistance development

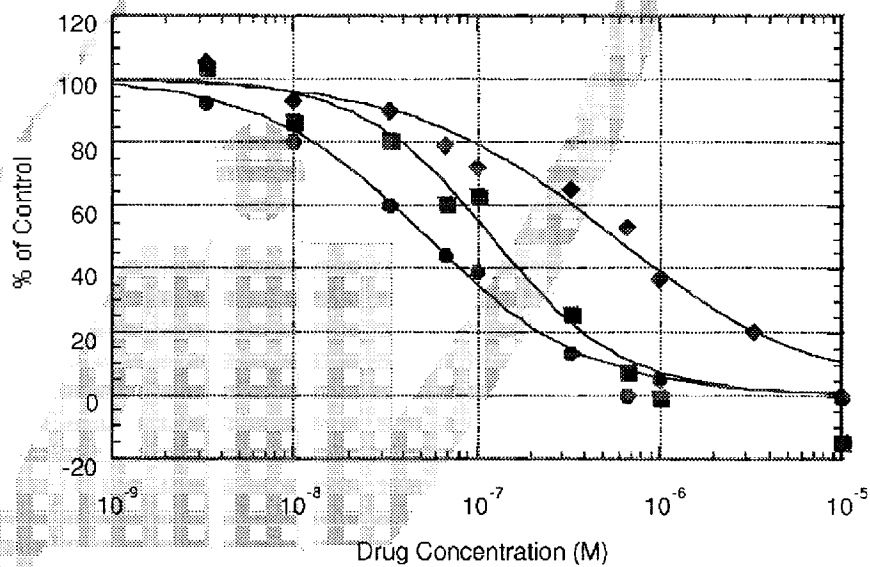
Microbiology

| Organism | MIC ₉₀ μ g/ml | | | |
|----------------------------|------------------------------|--------|-------|--------|
| | ABT-773 | Ketek | Clari | Azi |
| <i>S. pneumoniae</i> ery-S | 0.008 | 0.004 | 0.03 | 0.12 |
| <i>S. pneumoniae</i> mef | 0.12 | 1.0 | 4.0 | 16.0 |
| <i>S. pneumoniae</i> erm | 0.01 | 0.12 | >32 | >32 |
| <i>S. pyogenes</i> ery-S | 0.12 | 2.0 | 1.0 | 2.0 |
| <i>S. pyogenes</i> ery-R | 0.5 | >8.0 | >32 | >32 |
| <i>M. catarrhalis</i> | 0.25 | 0.25 | 0.5 | 0.25 |
| <i>H. Influenzae</i> | 2.0 | 2.0 | 16 | 2.0 |
| Legionella | 2.0 | 2.0 | 0.06 | 1.0 |
| <i>M. Pneumoniae</i> | <0.005 | <0.005 | 0.008 | <0.005 |
| <i>C. Pneumoniae</i> | 0.015 | 0.06 | 0.06 | 0.12 |





Ribosome Binding, Susceptible *S. pneumoniae*

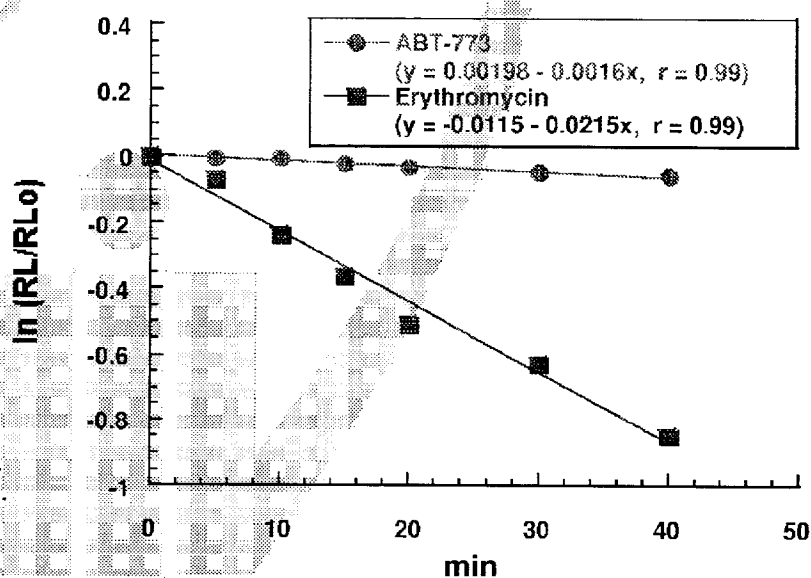


erythromycin (◆),
telithromycin (■),
ABT-773 (●).

IC₅₀ of Ery is 566
nM; telithromycin is
120 nM; ABT-773 is
52.7 nM. Abbott
Internal Data.



ABT-773 Displacement in Susceptible *S. pneumoniae* 2486



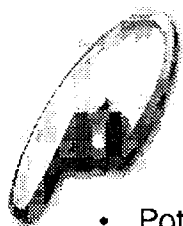
J. Capobianco et al.
ICAAC 1999, #2137.



QTc potential and Liver Toxicity Issues

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QTc Prolongation Issues

- Potential for QTc Prolongation is a hot button worldwide
 - Antimicrobial agents including macrolides and quinolones are of concern to regulatory agencies
 - CPMP guidelines require data from animal models and 200 subjects
 - FDA is in the process of evaluating all drug class known to have a potential for prolonging QTc (erythromycin and clarithromycin)
 - FDA has question whether ketolides behave like macrolides
 - FDA requested additional dog tox work to evaluate QTc
 - Required to include ECG monitoring in pivotal Phase 3 studies
 - FDA may require a Phase I study in patients with underlying cardiac disease
 - Some antimicrobials now contain warnings for QT prolongation
 - Telithromycin (Ketek) data residing at FDA
 - Advisory Meeting rescheduled to May 2001 probably not related to QTc concerns



QT_c Prolongation Issues ABT-773

- Pre-clinical data positive for QT_c dose response.
- A possible dose effect in Phase I at total daily dose ≥ 800 mg.
- No significant QT effect observed when ABT-773 was administered with the metabolic inhibitor ketoconazole. (Increased ABT-773 C_{max} 5X)
- No concentration response in Phase I studies (≤ 300 mg).
- No consistent QT effect observed at clinical doses studied in Phase IIB studies. (150 mg QD to 600 mg QD)



QT_c Prolongation Issues ABT-773 Plan

- Completed pre-clinical evaluation of ABT-773
- Completed ECG monitoring of >200 patients in Phase II and III
- Continue to monitor QTc and electrolytes in Phase III programs.
- Planning FDA requested study of QTc in patients with pre-existing cardiac disease.
- IV ABT-773 Phase I study will monitor QTc carefully
- Consult with Drs. Morganroth and Moss QTc advisors.



Liver Toxicity Issues

- **Potential for liver toxicity is a concern for the FDA**
 - Recent liver toxicity seen with Trovofloxacin are of concern to regulatory agencies.
 - Gemifloxacin recently not approved by FDA because of liver toxicity concerns.
 - FDA meeting on guides to industry on how to study liver function scheduled for February 11-12, 2001



Liver Toxicity Issues for ABT-773

- Preclinical tox showed some effect on the liver function.
- Japanese in bridging study showed increased LFTs.
- No evidence of LFT issue in Western subjects.
- No evidence of dose response.
- Repeat of Japanese bridging study in Japan showed No evidence of LFT increases in Japanese or Caucasians.
- ABT-773 plan for accessing problem
 - Continue to monitor LFT in Phase III programs.
 - Jean Fox will attend FDA meeting.

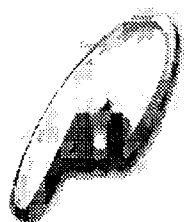


Phase III Program

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PART 5



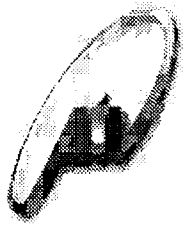
Phase III Program

Proposed Indications and Treatment Duration

| Infection | Dosage | Duration |
|------------------------------------------------------------|------------------|----------|
| Pharyngitis/Tonsillitis due to: | | |
| <i>S. pyogenes</i> * | 150 mg QD | 5 d |
| Acute bacterial sinusitis due to: | | |
| <i>H. influenzae</i> | 150 mg QD or BID | 10 d |
| <i>M. catarrhalis</i> | 150 mg QD or BID | 10 d |
| <i>S. pneumoniae</i> ** | 150 mg QD or BID | 10 d |
| Acute bacterial exacerbation of chronic bronchitis due to: | | |
| <i>H. influenzae</i> | 150 mg | 5 d |
| <i>I. parainfluenzae</i> | 150 mg | 5 d |
| <i>M. catarrhalis</i> | 150 mg | 5 d |
| <i>S. pneumoniae</i> ** | 150 mg | 5 d |
| Community-acquired pneumonia due to: | | |
| <i>C. pneumoniae</i> | 150 mg QD or BID | 10 d |
| <i>H. influenzae</i> | 150 mg QD or BID | 10 d |
| <i>L. pneumophila</i> | 150 mg QD or BID | 10 d |
| <i>M. pneumoniae</i> | 150 mg QD or BID | 10 d |
| <i>S. pneumoniae</i> ** | 150 mg QD or BID | 10 d |

* Including macrolide-resistant strains.

** Including penicillin-resistant and macrolide-resistant strains.



Phase III Program *Studies Started in Year 2000*

| Study | Indication | ABT-773 Regimen | Comparator | Number Subjects | Location |
|---------|-------------|------------------------|--------------|--------------------|-------------------|
| M00-223 | Pharyngitis | 150 mg QD 5 days | Penicillin V | 185/520 | US (IND) |
| M00-222 | Pharyngitis | 150 mg QD 5 days | Penicillin V | 0/520 | EU (Non-IND) |
| M00-216 | ABECB | 150 mg QD 5 days | Azithromycin | 131/600 | US, Canada IND |
| M00-217 | ABECB | 150 mg QD 5 days | Levofloxacin | 0/500 | EU (Non-IND) |



Phase III Program

Studies Started in Year 2000, Con't

Dose Finding Studies for Sinusitis/CAP:

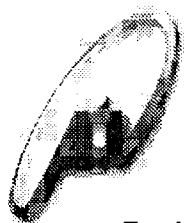
| Study | Indication | ABT-773 Regimen | Comparator | Number Subjects | Location |
|--------------|-------------------|----------------------------------------|-------------------|----------------------------|----------------------------|
| M00-225 | Sinusitis | 150 mg QD vs. 150 mg BID 10 days | None | 137/500 | US, EU (IND) |
| M00-219 | CAP | 150 mg QD vs. 150 mg BID 10 days | None | 76/500 | US, Canada, EU (IND) |



Dosing Issue

150 mg BID vs 150 mg QD: Background

- Phase II data indicated 300 mg QD was not viable due to high levels of diarrhea (10-20%) and taste perversion (10-20%)
- Phase II ABECB and pharyngitis/tonsillitis data supported 150 mg QD
 - 150 mg QD currently being evaluated in ongoing phase III trials in these indications
- Dosing selection for CAP and sinusitis confounded by limited data
 - few bacterial isolates, particularly with H. flu in sinusitis
 - no 150 mg arm in CAP trial
- To increase probability of correct dose selection in CAP/sinusitis, the decision was made to undertake additional studies to generate more data in these indications
 - 150 mg QD vs 150 mg BID CAP & sinusitis trials ongoing
 - Decision facilitated by Decision Support Group, with joint AI & PPD consensus on decision



Dosing Issue

150 mg BID vs 150 mg QD: Implications of Decision

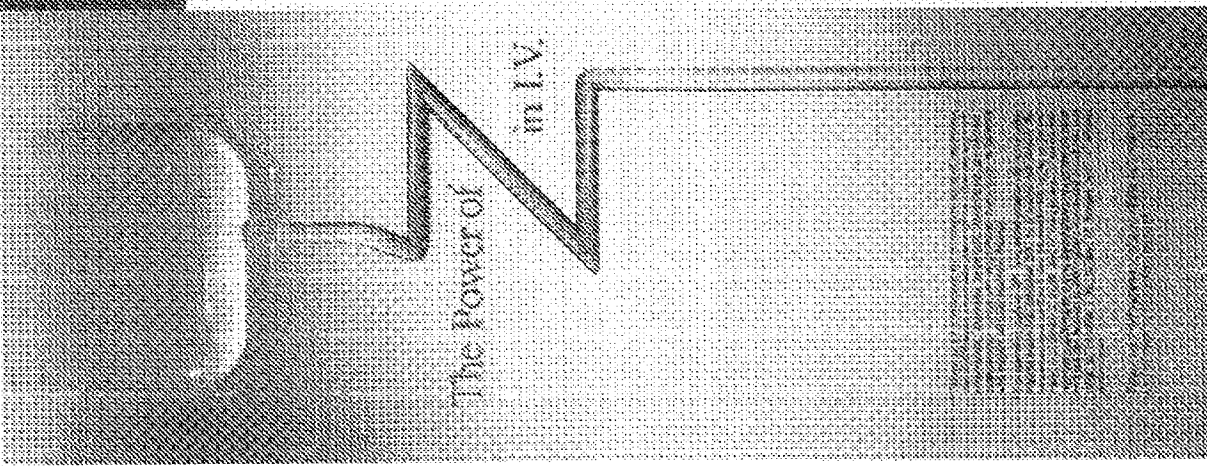
- **For U.S. market:**
 - Absence of consistent QD dosing for all indications represents a significant commercial hurdle
 - Approval on indication-by-indication basis
 - Optimal strategy for U.S. may be to pursue QD dosing for CAP/sinusitis
- **For ex-U.S. market:**
 - CAP data represents the "lynchpin" for approvability of the entire molecule, hence a conservative BID approach may result in lower regulatory/commercial risk
 - Relatively minor commercial impact of BID dosing
 - Optimal strategy for ex-U.S. may be to pursue BID dosing for CAP and perhaps sinusitis
- **A decision of 150 mg QD vs 150 mg BID in CAP & sinusitis will be made based on phase III data 2Q01**
 - Key ex-U.S. criteria for CAP approval include: a) satisfactory efficacy/eradication in severe CAP b) sufficient resistant isolates with satisfactory eradication c) treatment of bacteremic cases
 - data may not show a clear "winner" due to relatively low power of studies; may be a difficult decision
 - due to soft global flu season and protocol amendments, enrollment is behind plan and could impact timing of decision
- **A plan to have divergent clinical programs in CAP/sinusitis may be an option**



ABT-773 IV Program

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ABT205071



**Once-daily
Zithromax I.V.**
azithromycin for injection

The only I.V. azithromycin preparation,
Zithromax I.V. provides the most powerful
coverage in adult hospitalized patients
with pneumonia.

| Target | Aspirin |
|--------------------------|-----------|
| Streptococcus pneumoniae | Excellent |
| Haemophilus influenzae | Excellent |
| Legionella pneumophila | Excellent |
| Mycoplasma pneumoniae | Excellent |
| M. tuberculosis | Excellent |

Proven, effective as
adjuvant therapy for pneumonia.

Early step-down therapy to oral Zithromax
may well be indicated.

Because Zithromax I.V. is a broad-spectrum antibiotic, it will cover
all the major organisms causing pneumonia, including
Streptococcus pneumoniae, Haemophilus influenzae, Legionella
pneumophila, Mycoplasma pneumoniae, and Chlamydia pneumoniae.
Zithromax I.V. is also effective against atypical organisms,
including Mycoplasma pneumoniae, Chlamydia pneumoniae,
and Legionella pneumophila.

Zithromax I.V. is a broad-spectrum antibiotic, it will cover
all the major organisms causing pneumonia, including
Streptococcus pneumoniae, Haemophilus influenzae, Legionella
pneumophila, Mycoplasma pneumoniae, and Chlamydia pneumoniae.

**Once-daily
Zithromax I.V.**
azithromycin for injection

The Power of Z in I.V.

**Once-daily
Zithromax I.V.**
azithromycin for injection

The Power of Z in I.V.



ABT-773 IV Formulation Strategic, Commercial, and Technical Value

- **Strategic Value**
 - IV represents a channel not currently served by Anti-infective Franchise
 - Leverages presence of Medical Center Reps and experience with ID community
- **Commercial Value**
 - IV availability figures favorably into decisions regarding formulary access to molecule
 - potential advantage over telithromycin, which will not have an IV
 - required to compete effectively with Zithromax, Tequin, Avelox which have IVs
 - Positive impact on tablet formulation
 - estimated \$36MM incremental to peak tablet sales due to step-down therapy
 - Enhances overall "potency" image of brand
- **Technical Value**
 - Support for *S. pneumoniae* Resistance claim
 - FDA indicated that bacteremic patients will be important to establish body of evidence for this claim
 - Provides additional information on QT effects

IV launch currently lags tablet launch by 1 year; any further delays will reduce the potential value



ABT-773 IV Program Formulation Objectives

- Reconstituted solution . Once a day dosing. Low pain on injection
- Lyophilized powder, consisting of ABT-773 and a counter ion base.
- One strength, in a flip-top vial and the ADD Vantage system at launch.
- Diluent volume 100ML, with length of infusion (30 to 60 minutes) and type of diluent (Dextrose 5% and/or normal saline) TBD based on animal pain models, clinical and stability studies.



ABT-773 IV Formulation PPD/HPD Funding Status

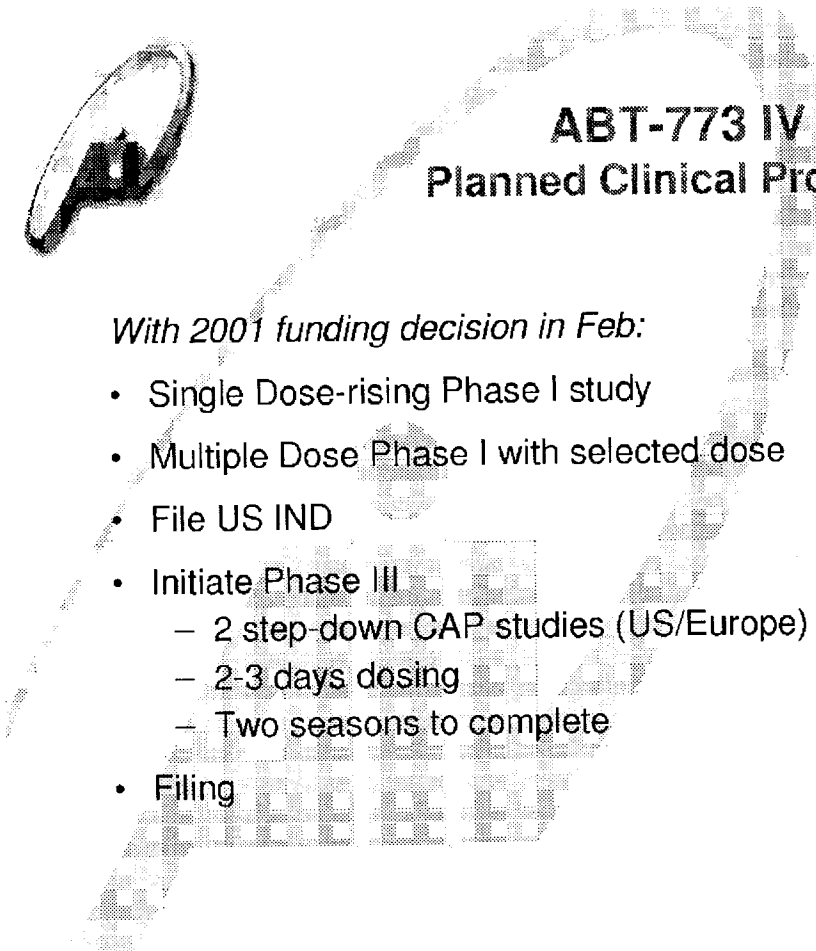
- PPD/HPD Collaboration initiated 9/99
- PPD funded Program 01/00-08/00 (\$1.4MM)
 - Formulation development (lactate salt, lyophilized powder)
 - Animal pain models
 - Two week Tox study (monkey)
- HPD funded Program 08/00-12/00 (\$0.8MM)
 - Two week Tox study (rat)
 - Clinical supplies for Phase I
 - Stability program
- 2001 funding
 - HPD first pass funding cut for 773 IV (\$7MM)
 - Milestone funding to Phase I Go/No Go (\$1MM)
- Total program development costs 2000 - 2003 (\$22.5MM)



ABT-773 IV Formulation

Animal Pain Study Results

- Assessed 6 prototypes (3 different counter ions at 2 pH levels) vs clarithromycin IV and azithromycin IV
- Animal pain models showed no differentiation among all three compounds
 - Results not conclusive
 - Need to evaluate in humans
- Chose ABT-773 lactate as the prototype to test in Phase I studies based on manufacturability and stability.



ABT-773 IV

Planned Clinical Program

With 2001 funding decision in Feb:

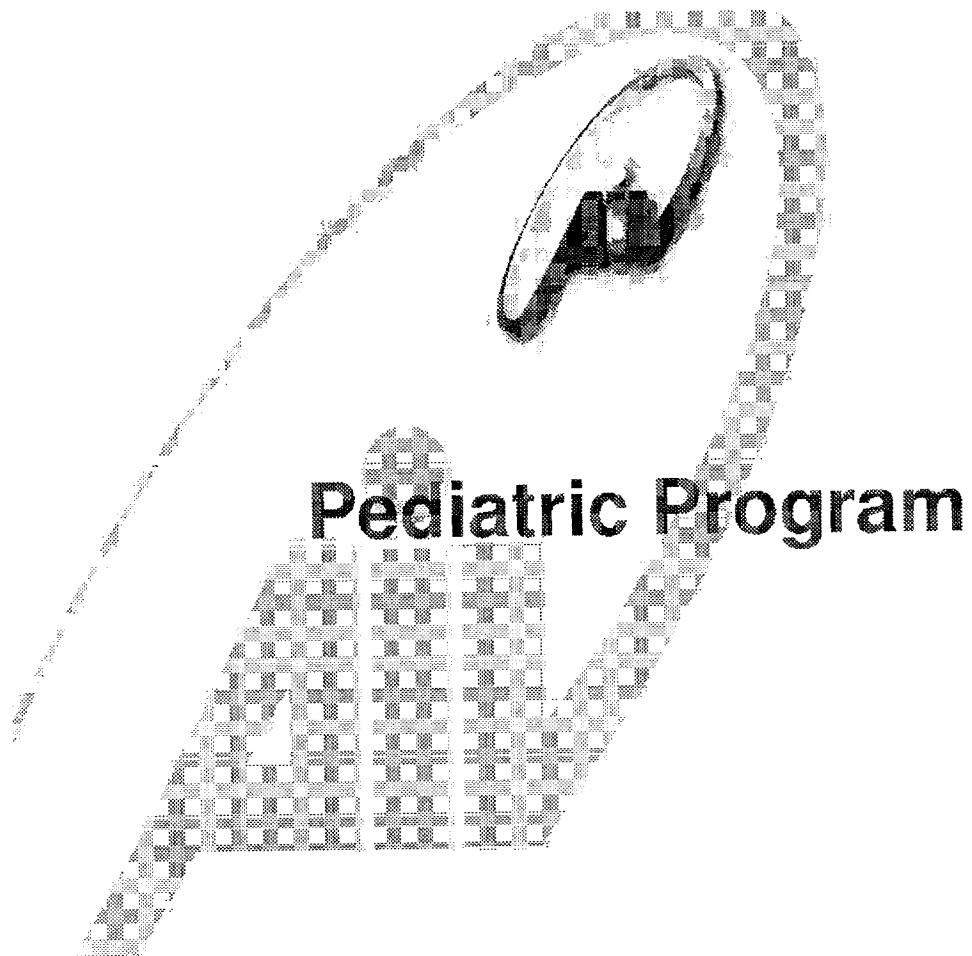
- | | |
|--------------------------------------------|---------|
| • Single Dose-rising Phase I study | Apr/01 |
| • Multiple Dose Phase I with selected dose | June/01 |
| • File US IND | Oct/01 |
| • Initiate Phase III | Dec/01 |
| – 2 step-down CAP studies (US/Europe) | |
| – 2-3 days dosing | |
| – Two seasons to complete | |
| • Filing | Aug/03 |



ABT 773 IV Program Summary

- **Comments**

- Funding for '01 not available PPD/HPD
- Go/No go could be made after Phase I based on safety profile (pain,QT,GI)
- Milestone funding recommended (\$1MM)
- Assuming Go, '01 budget estimated \$7MM
- IV will help to obtain resistant *S. pneumo* claim
- Total Program Cost 2000-2003 (\$22.5MM)



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ABBT205079



ABT-773 Pediatric Formulation

Importance to the 773 program

- Increased perception of safety
- Better pricing and acceptance in European markets
- FDA requires studies in pediatrics



ABT-773 Pediatric Program Formulation Objectives

- Develop coated particle formulae for global use
 - coated particles for Suspension - 150mg/5mL & 300mg/5mL
 - coated particles as a dry syrup, sprinkle or sachet.
- Desired Properties
 - Once a Day Dosing
 - Acceptable 'Initial Taste'
 - Minimal 'After Taste'
 - No Unpleasant Mouth-feel
 - Acceptable Color and Flavor
 - No Refrigeration Required.



ABT 773 Pediatric Program Taste Assessment

Sensory Analysis of Uncoated Drugs *Summary of Results*

The three drug substances can be ranked from most to least bitter as follows:

| Drug Substance | Concentration (ppm) Which Exhibits an Initial Bitter Intensity ≤ 1 (Slight) |
|-----------------------|----------------------------------------------------------------------------------------------------|
| ABT-773 | 0.79 |
| Clarithromycin | 4.2 |
| Azithromycin | 15 |

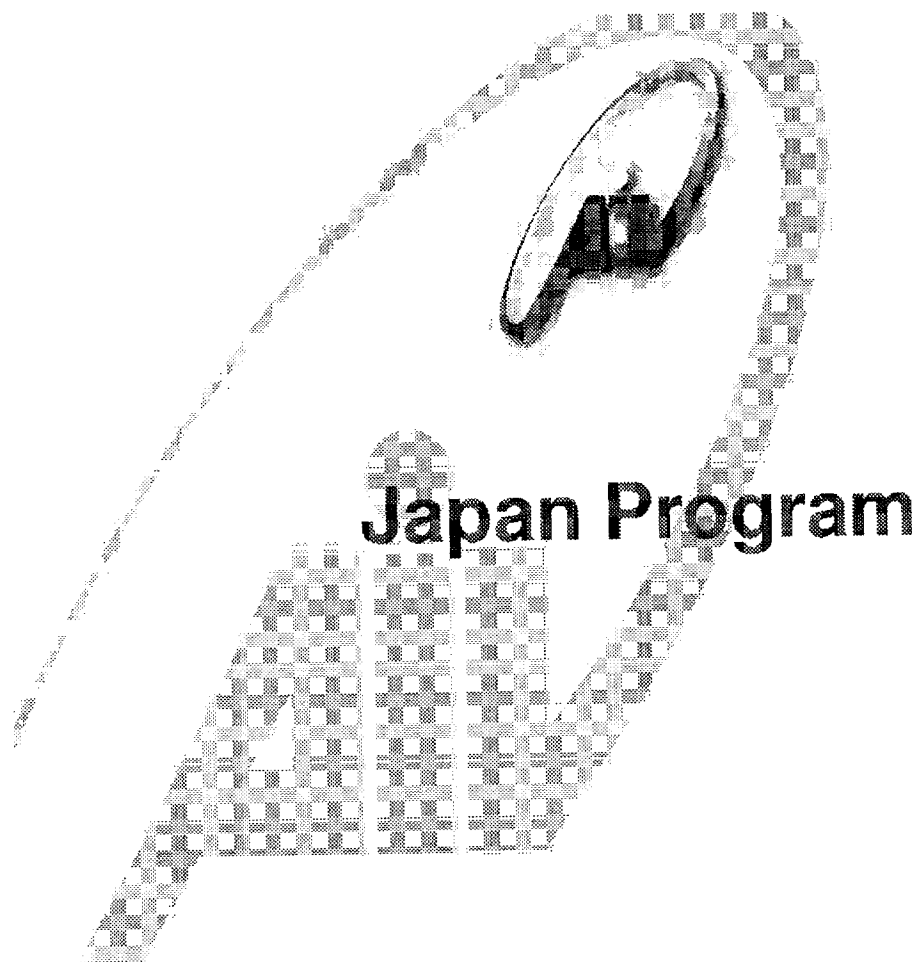
- ABT-773 is approximately five times more bitter than clarithromycin



ABT 773 Pediatric Program

Taste Assessment

- The ABT-773 encapsulated prototype #2 may be at risk of dosing compliance problems due to flavor quality.
- Overall ABT-773 Prototype 2
 - Less bitter than Biaxin both initial and after taste
 - More bitter than Zithromax both initial and after taste
- For ABT-773 Prototype 2, the flavoring aromatics and sweetness decay quickly, exposing the bitterness which lingers throughout the aftertaste at or above the “concern” intensity level.



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ABBT205084



Japan Program Taisho

- Japan development is planned in coordination with Taisho and Dainabot
- Meetings are held at least 3 times a year to review developments
- Taisho funds 10.69% of global development costs and 50% of local Japan costs.
- Bridging strategy is primary plan for development in Japan



Japan Program Clinical Plan

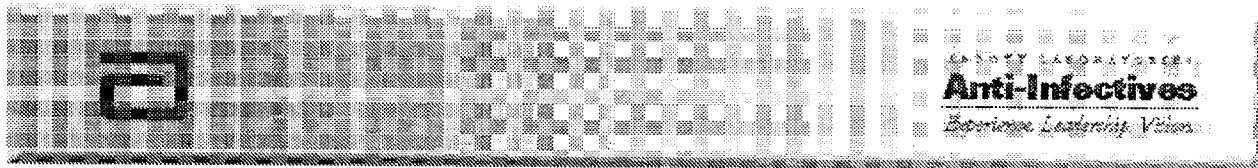
- Phase I in Japan
 - Food Effect Study Start
Completed
 - Single and multiple dose study Completed
 - Review data (Abbott/Taisho) April/01
 - PK data Japanese vs Caucasian
 - Development program strategy
 - Present Kiko data and recommend development program
 - May/01
 - Start Tissue Conc. Study 2Q/01



Japan Program Clinical Plan

- PK similar in Japanese and Caucasians (12/02 filing)
 - Recommend to Kiko same dose in Japan as in ex-Japan
 - Recommend to Kiko one comparative bridging study in CAP (Phase III) and several smaller local studies in skin infections, dentistry, otolaryngology, UTI and pan-bronchiolitis
 - Taisho agreement necessary prior to Kiko meeting
- PK different in Japanese and Caucasians (12/03 filing)
 - Phase II dose ranging study in CAP (Bridging study)
 - Phase III comparative study will be required
 - Full development time line
 - Implications on Taisho cost-sharing

ABT-773 Portfolio Review
December 5, 2000



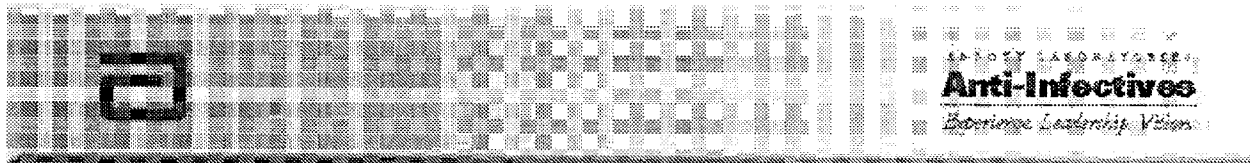
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Agenda

Part 1: General Overview, Tablet

-
- **Introduction-Carl Craft (5 min)**
 - **Executive Summary-George Aynilian (10 min)**
 - **Anti-Infective Market/Commercial Rationale-Rod Mittag (15 min)**
 - **Microbiology-Bob Flamm (20 min)**
 - **Tablet Clinical Program**
 - Phase II data-Joaquin Valdes (20 min)
 - Phase III clinical plan-Joaquin Valdes (10 min)
 - **SPD Summary-Ashok Bhatia (10 min)**
 - **Tablet Key Issues**
 - Analysis of QT/Liver data-Dave Morris (20 min)
 - PK profile-Linda Gustavson (10 min)
 - Regulatory-Jeanne Fox (10 min)
 - Timeline risk George Aynilian (5 min)
 - **Tablet Commercial Profile, Strategy & Financials-Rod Mittag (10 min)**



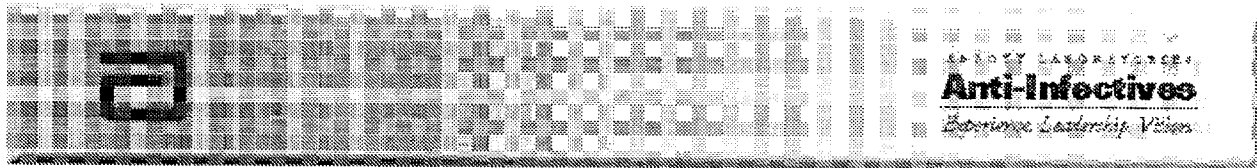
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Agenda

Part 2: I.V., Pediatric, Japan, Q&A

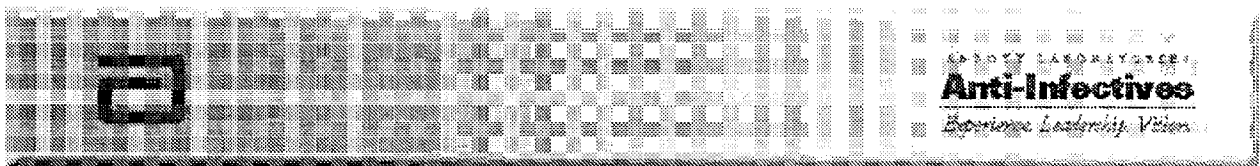
-
- I.V. Program/Issues-Carol Meyer (5 min)
 - Pediatric Program/Issues-Carol Meyer (5 min)
 - Japan Program/Issues-Carol Meyer (5 min)
 - ABT-492 (time permitting)
 - timeline
 - budget
 - rationale
 - Summary-Carl Craft (5 min)
 - Q&A



ABT-773***Executive Summary***

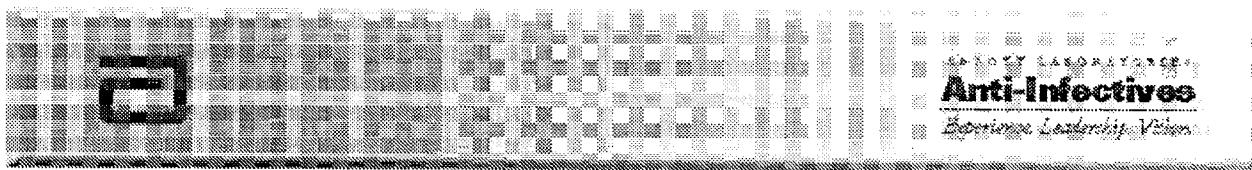
- **Management**

- Established European Clinical Team (11 dedicated members)
- Plans ongoing to strengthen Japan team
- Completed staffing of Abbott Park team
- Established communication team
- Completed conceptual model of study tracking application (web based)
- Established integrated project management system



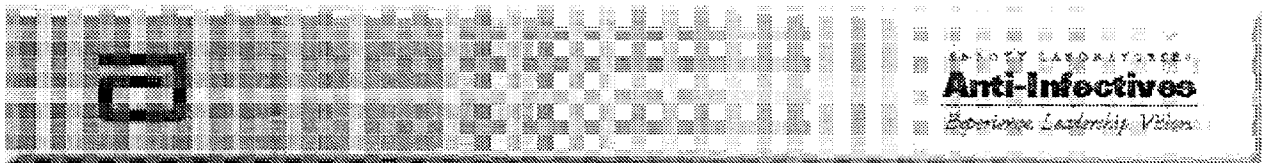
ABT-773
Executive Summary

-
- **Chemistry**
 - Exceeded '00 goals for yield, cost/Kg and deliveries
 - Task Force implemented modification of 3 steps
 - 3 TPMs for intermediates well established
 - Prepared package for justifying Step 5 as starting material



ABT-773***Executive Summary***

-
- **Tablet Formulation**
 - Scale up operations at AP and IDC on target
 - Linkage of materials between scales and sites being established by bioequivalency trials.
 - NDA runs and stability were initiated for 08/02 filing.



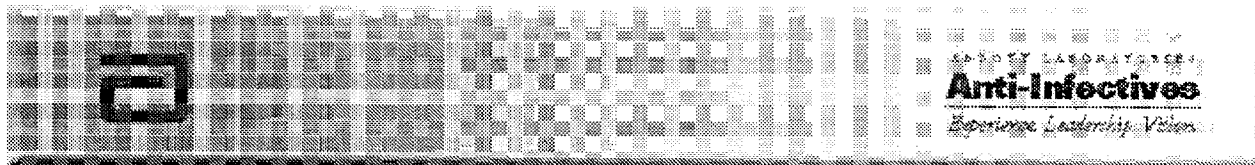
ABT-773
Executive Summary

- **IV Formulation**

- Clinical supplies complete. Tox. program ongoing. Phase I planned for 1Q '01.

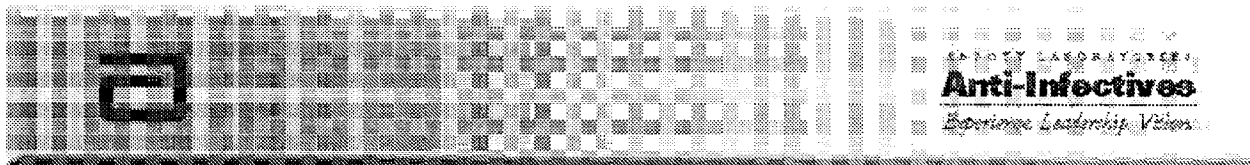
- **Pediatric formulation**

- Phase I complete with two prototypes. After- taste an issue. Formula optimization required. Pro-drugs under consideration. No funding in '01 plan budget



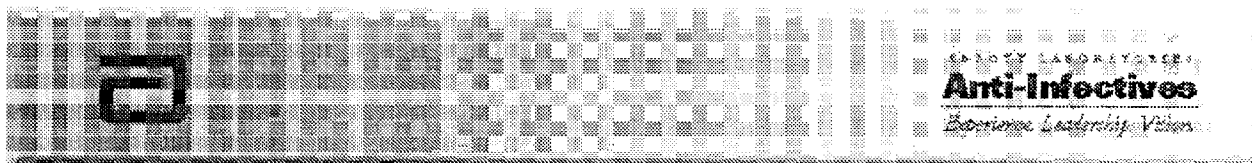
ABT-773
Executive Summary

- **Preclinical Safety**
 - Dog model (IV infusion) and Purkenje fiber studies completed as part of effect of drug on QTc. Additional study planned per EOPII meeting with FDA.
- **Molecular Biology**
 - Extensive work on ribosomal binding completed. Preliminary results published. Additional studies ongoing.



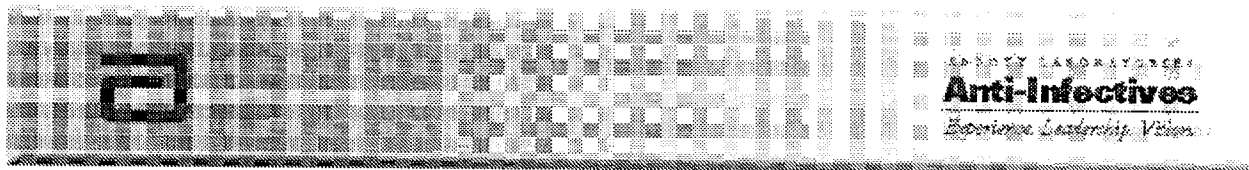
ABT-773
Executive Summary

- **Clinicals**
 - Completed Three Phase IIb studies
 - Decision Support Analysis completed
 - Dose selection 150mg and 150mg bid
 - Initiated Phase III program(6 studies, 4 under IND)
 - Completed all Investigator's meetings
 - Regulatory meetings
 - UK, Germany, France, US
- **End of Phase II package**
 - Document sent to FDA X/X
 - End of phase II meeting held with FDA 11/26
- **Japan bridging study/Kiko Mtg/Repeat Phase I in Japan**



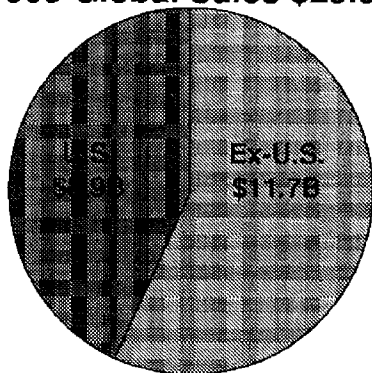
ABT-773
Executive Summary

- **Key Events (Nov '00-June '01)**
 - Initiate Phase III (ABECB, ASP, ABS, CAP) in US/EU
 - End of Phase II meeting with FDA (New amendment, informed consent)
 - Initiate Japan Phase I program in Japan
 - Results of Phase III (CAP/ABS) studies
 - Selection of regimen between 150mg QD and 150mg BID for CAP/ABS.
 - Set up balance of Phase III studies (CAP/ABS) 4 studies

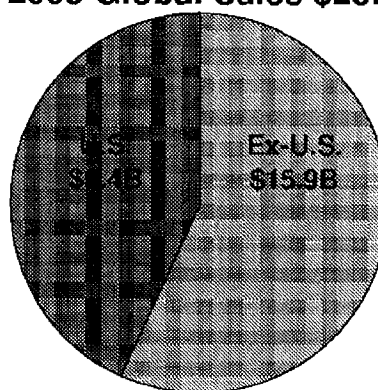


Global Antibiotic Market Sales
Current vs Future Projection

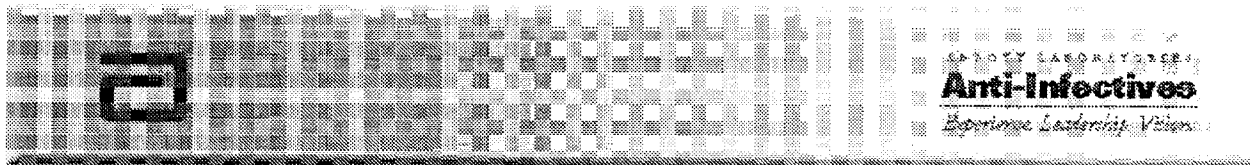
1999 Global Sales \$20.6B



2005 Global Sales \$25.3B

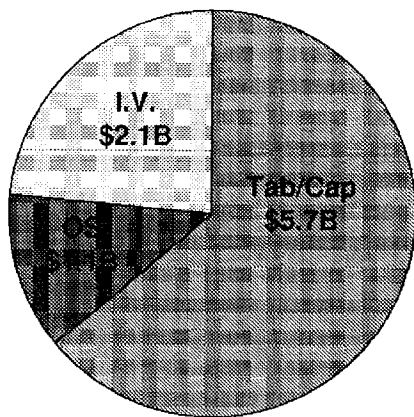


The antibiotic market is a large market and is expected to expand on a global sales basis

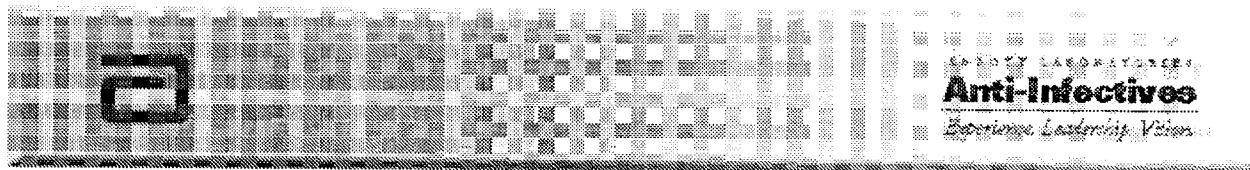
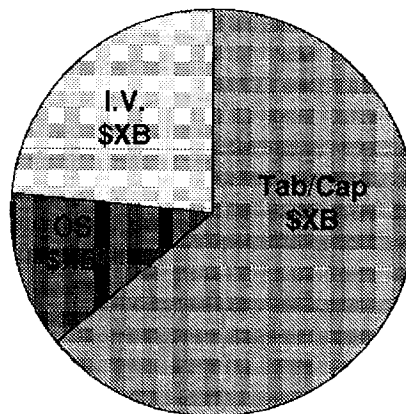


Global Antibiotic Market Sales
by Formulation

1999 U.S. Sales \$8.9B



1999 Ex-U.S. Sales \$11.7B



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ABBT205099

Key Competitors

U.S. Market

| Franchise | Macrolides | Quinolones | Beta-Lactams | Other | Injectables* |
|-----------------------------------|------------|------------|--------------|---------|--------------|
| Abbott | \$856 | \$740 | \$46 | \$3 | \$165 |
| Pfizer | \$1,396 | \$1,076 | \$71 | \$3 | \$213 |
| SB | \$1,303 | | \$1,229 | | \$74 |
| Bayer | \$1,034 | | \$911 | \$1 | \$122 |
| J&J | \$797 | | \$612 | | \$185 |
| Roche | \$526 | | | \$10 | \$518 |
| Glaxo | \$551 | | \$6 | \$425 | \$28 |
| BMS | \$387 | | \$1 | \$386 | |
| Lilly | \$107 | | \$33 | | \$74 |
| Others | \$1,670 | \$95 | \$27 | \$631 | \$298 |
| '99 Total | \$6,790 | \$1,911 | \$1,628 | \$2,755 | \$343 |
| | | | | | \$2,153 |
| '98 Total | \$7,570 | \$1,592 | \$1,331 | \$2,453 | \$272 |
| % Chg | 16.12% | 20.04% | 22.31% | 12.31% | 26.10% |
| | | | | | 12.02% |
| TY vs LY | | | | | |
| * Includes IV form of all classes | | | | | |
| Source: IMS | | | | | |

Ex-U.S. Market

| Franchise | Macrolides | Quinolones | Beta-Lactam | Injectables | Other |
|---------------------|------------|------------|-------------|-------------|---------|
| Abbott | \$ 717 | \$679 | \$ 22 | \$ 3 | \$ 13 |
| Shionoi Seiyaku | \$ 959 | \$ 2 | \$ 3 | \$ 432 | \$ 466 |
| Pfizer | \$ 664 | \$267 | \$ 12 | \$ 68 | \$ 245 |
| SKR | \$ 842 | \$ 0 | \$ 0 | \$ 780 | \$ 61 |
| BMS | \$ 547 | \$ 0 | \$ 2 | \$ 378 | \$ 154 |
| Roche | \$ 460 | \$ 0 | \$ 3 | \$ 43 | \$ 303 |
| Bayer | \$ 524 | \$ 0 | \$437 | \$ 43 | \$ 43 |
| Lilly | \$ 437 | \$ 28 | \$ 0 | \$ 337 | \$ 66 |
| Fujisawa Yakuhin | \$ 522 | \$ 0 | \$ 0 | \$ 411 | \$ 111 |
| Daiichi Seiyaku | \$ 497 | \$ 0 | \$487 | \$ 0 | \$ 0 |
| '99 Sub-total | \$6,178 | \$977 | \$376 | \$2,495 | \$1,461 |
| | | | | | \$269 |

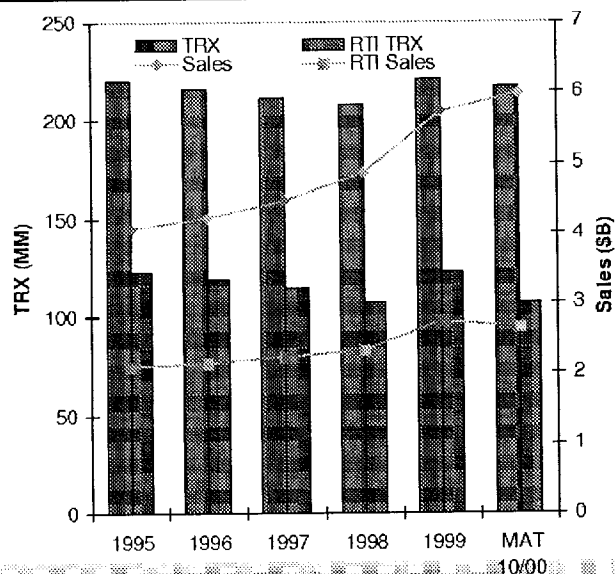


ANTHONY LABORATORIES
Anti-Infectives
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PART 6

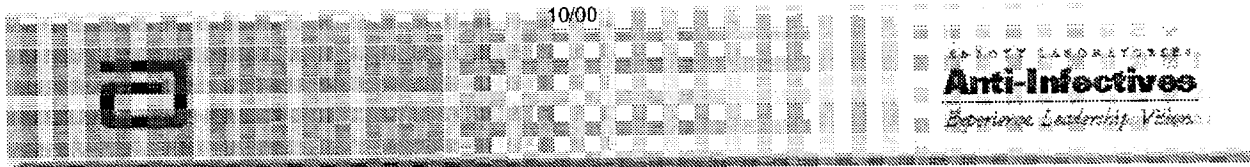
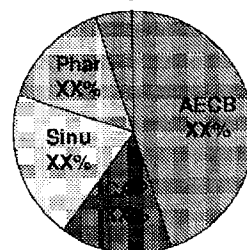
U.S. Tab/Cap Antibiotic Market

TRX & Sales Trends

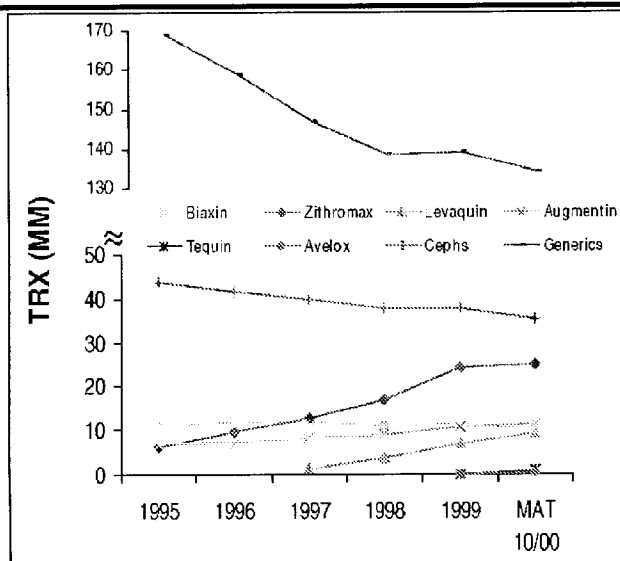


- While negative pressure exists on antibiotic usage, market sales have increased substantially
- TRX CAGR₉₅₋₉₉ = + 0.1%
- Sales CAGR₉₅₋₉₉ = + 8.9%

RTI Sales by Indication



U.S. Tab/Cap Antibiotic Market Product Trends

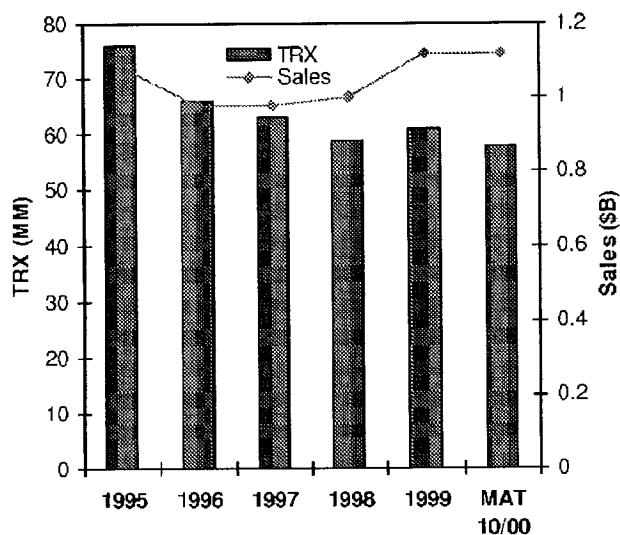


- Market sales increases being driven by replacement of older/cheaper agents with branded agents
- Zithromax has driven market demand for cost/convenience/tolerability
- Quinolones (Levaquin, Tequin, Avelox) are fastest growing segment, playing into resistance concerns; 1998-99 growth of 15% (TRX) & 22% (\$)



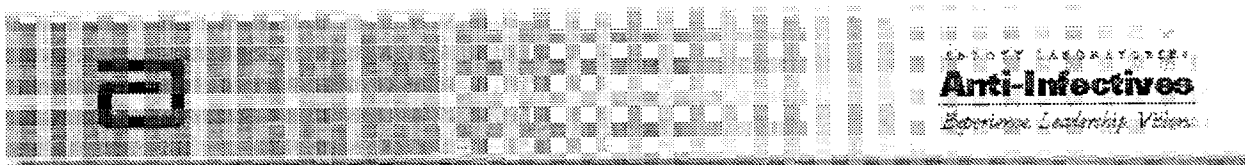
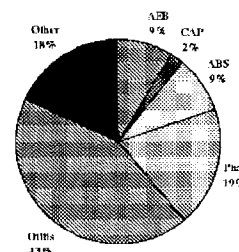
EMERY LABORATORIES
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U.S. Pediatric Antibiotic Market TRX & Sales Trends

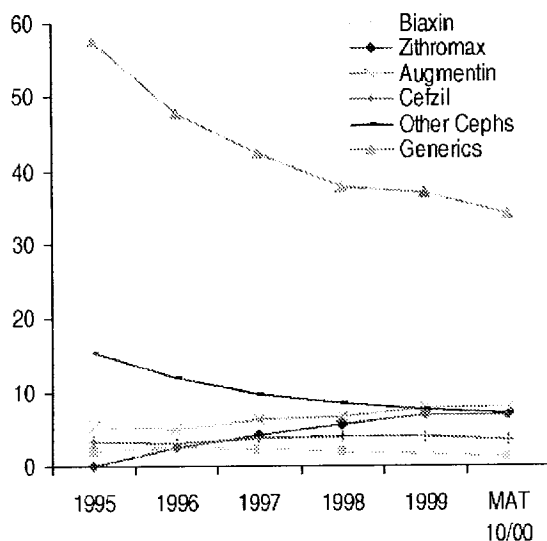


- TRX CAGR₉₅₋₉₉ = - 5.4%
- Sales CAGR₉₅₋₉₉ = + 1.0%
- TRX under greater pressure than Tab/Cap market
- Recent leveling in sales

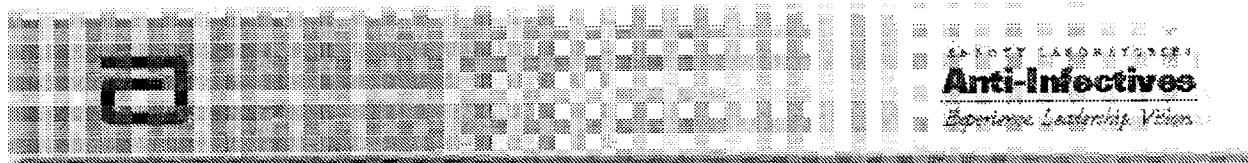
Sales by Indication



U.S. Pediatric Antibiotic Market Product Trends



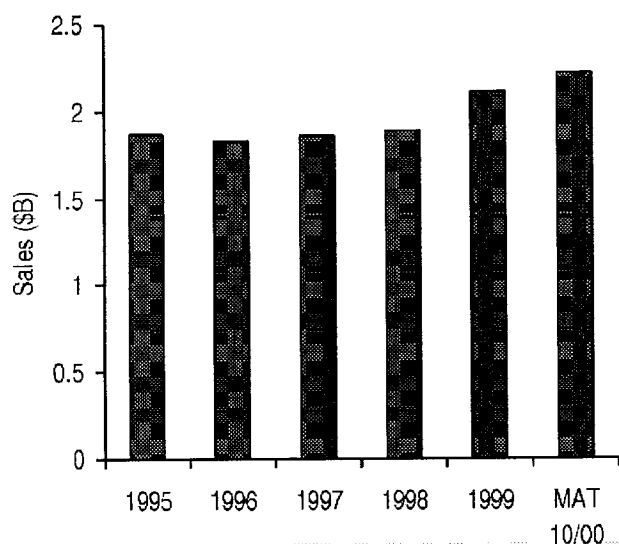
- Market sales increases being driven by replacement of older/cheaper agents with branded agents
- Taste and convenience are key market drivers
- Key branded products (Zithromax, Cefzil) lose patent exclusivity in 2005 timeframe
- May be opportunity for ABT-773, as resistance is substantial in this population; also conveys positive "safety" image to brand



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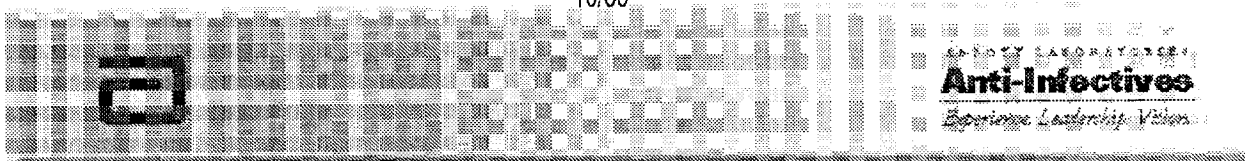
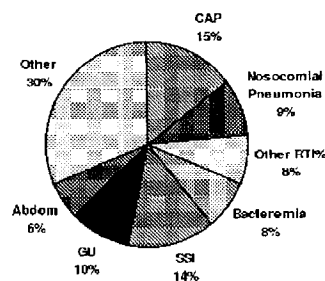
ABBT205104

U.S. Injectable Antibiotic Market Sales Trends

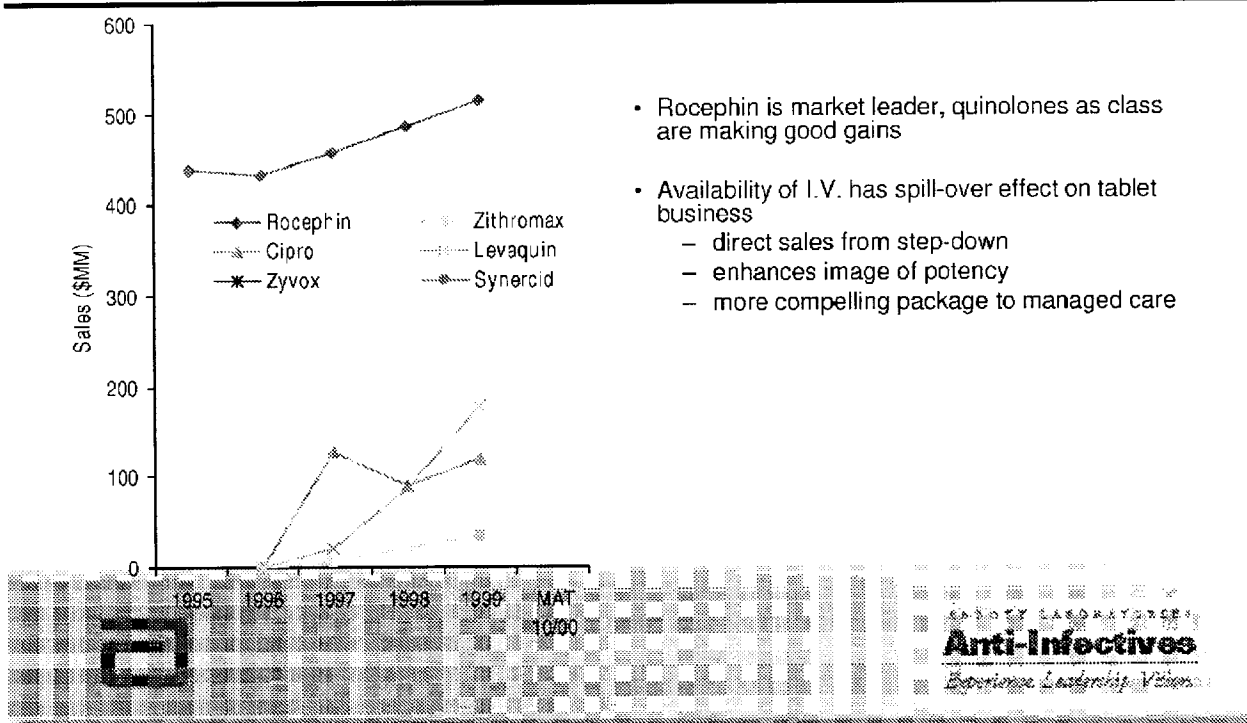


- **Current Market: \$2.1B, CAGR = + 3.2%**
- **Two market segments:**
 - Severe community-acquired
 - Rocephin, Levaquin, Tequin, Zithromax
 - Nosocomial
 - Synercid, Zyvox, vancomycin

Uses by Indication



U.S. Injectable Antibiotic Market Product Trends



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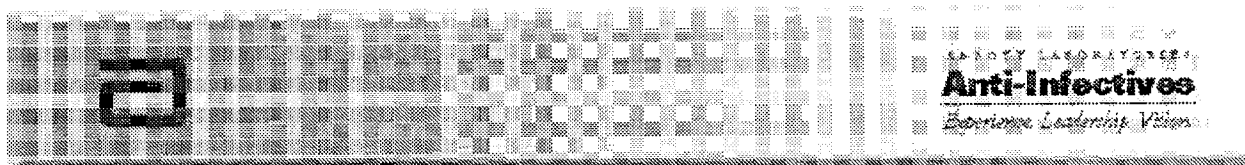
ABBT205106

Global Market Drivers

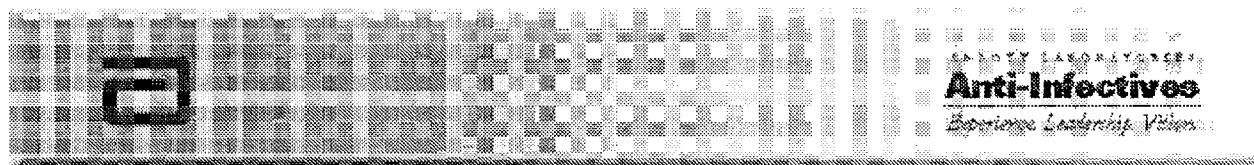
Negative vs Positive Drivers

-
- Antibiotic Resistance
 - Increasing sensitivity toward "appropriate use" may have negative impact on usage ⬇
 - Requires new agents to keep ahead of resistant pathogens; substitution of older generic agents with newer branded agents ⬆
 - Patent Expirations
 - May increase price sensitivity and bargaining power of MCOs ⬇
 - Use of generic agents tend to decrease over time; obsolescence/resistance may further that trend ⬆
 - Market expansion ex-US ⬆
 - Unmet Need ⬇
 - Overall unmet need relatively low
 - Cost, convenience, tolerability take on added importance
 - Increasing use of "implied efficacy" metrics i.e. MICs, resistance surveillance, AUC/MIC, MPC, kill kinetics
 - Competition ⬇
 - 5 NDAs/approvals in last 12 months; Avelox, Tequin, Factive, Spectracef, Ketek, Zyvox
 - Continued discovery/development activity by key competitors
 - High level of promotional activity

Negative driver ⬇
Positive driver ⬆



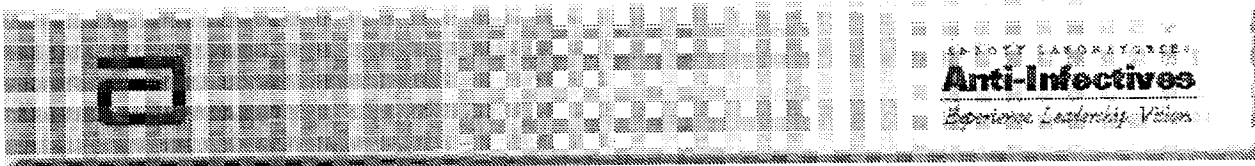
-
- Resistance surveillance



Patent Expirations
Expiration & At Risk Sales

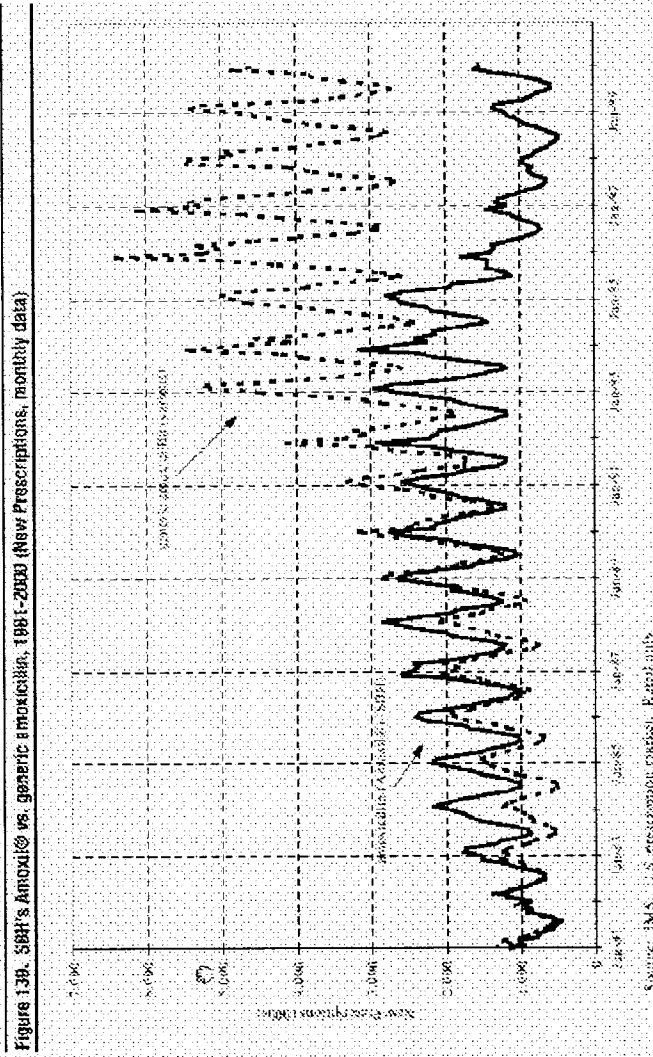
| | <u>Year</u> | <u>1999 U.S. Sales</u> <u>(\$MM)</u> |
|-----------|-------------|-----------------------------------------|
| Ceftin | 2003 | \$425 |
| Cipro | 2003 | \$1,023 |
| Biaxin | 2005 | \$756 |
| Cefzil | 2005 | \$357 |
| Levaquin | 2005 | \$708 |
| Zithromax | 2005 | \$1,111 |

\$5,540



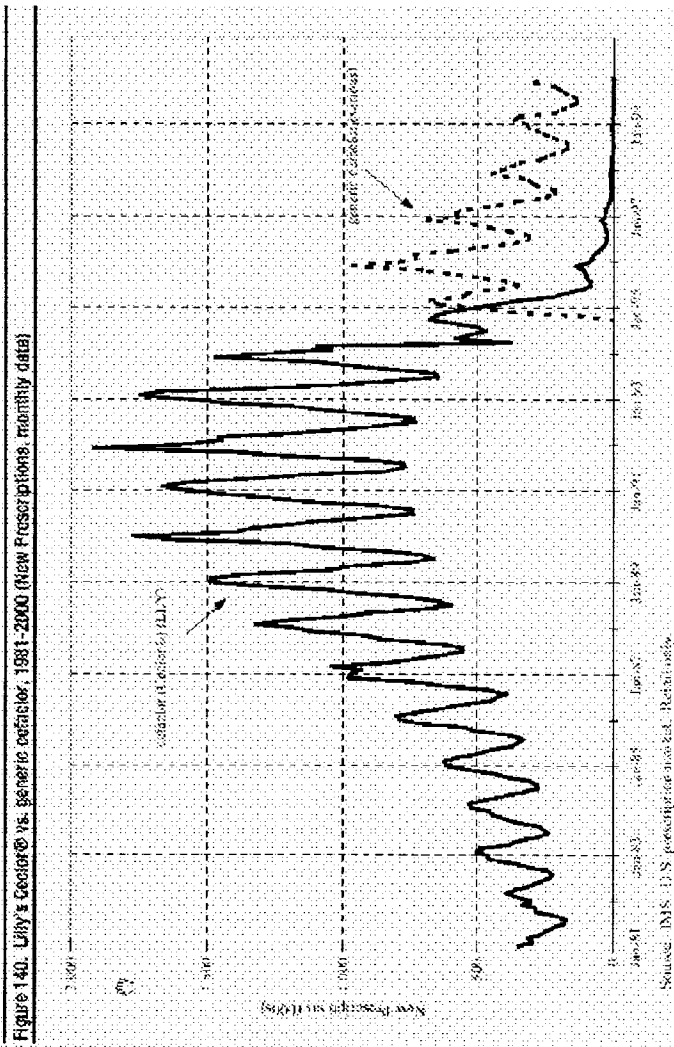
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ABRT205109



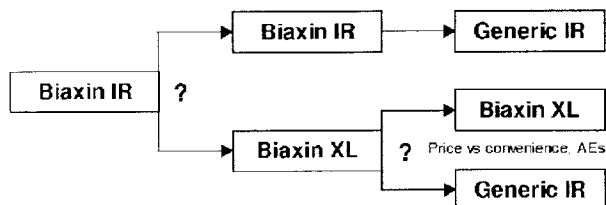
Anti-Infectives
Exposure Leadership Vision





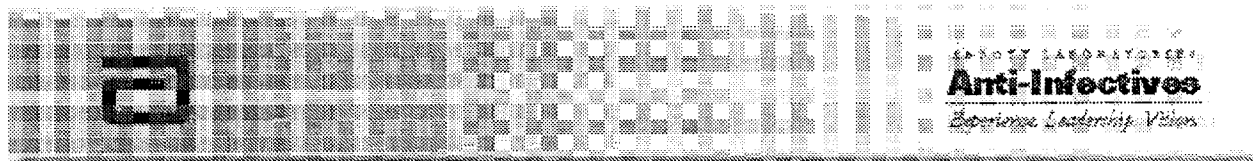
Anti-Infectives
Excellence in Medicine

Biaxin Patent Expiration Biaxin/773 Scenarios



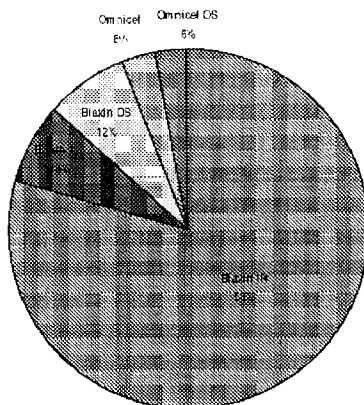
| | | XL==> Generic Conversion | | |
|----------------------|------|--------------------------|-----|------|
| | | Low | Med | High |
| IR ==> XL Conversion | Low | ? | C | C |
| | Med | | ? | C |
| | High | | | ? |

C = Convert Biaxin to ABT-773
Assumes high conversion rate of IR
to generics

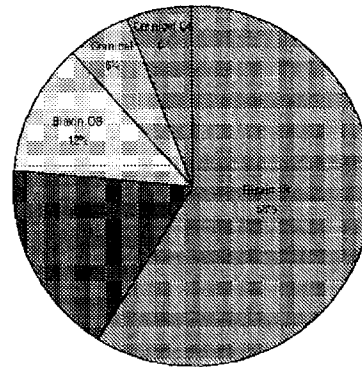


Abbott Anti-Infective Franchise
2001 Plan

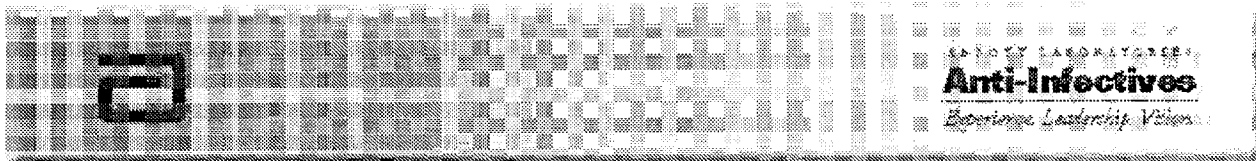
U.S. Sales = \$794 MM



Ex-U.S. Sales = \$XXX MM

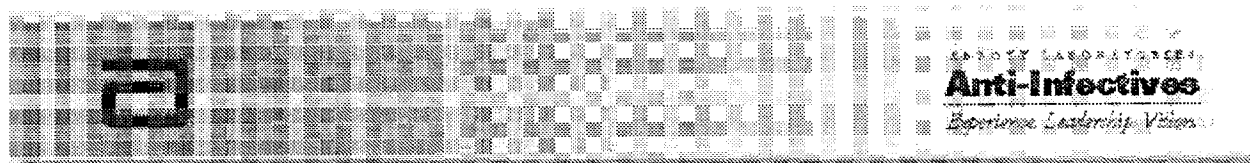


The global Anti-Infective portfolio is heavily dependent upon Biaxin; ABT-773 represents a key program given the Biaxin patent expiration in 2005



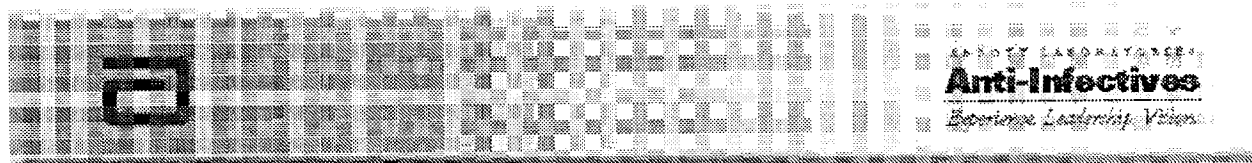
ABT-773 Profile

| | Current Profile |
|-------------------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Dosing | 150 mg QD x 5 d for ABECB & pharyngitis (1-pack) 150 mg QD or BID x 10 d for CAP & ABS (2-pack if QD) |
| Efficacy | ABECB: 87% Cure, 86% Eradication (150 mg QD) ABS: 89% Cure, 77% Eradication (150 mg QD) CAP: XX% Cure, XX% Eradication (300 mg QD) Pharyngitis: No clinical data, need > 85% for indication |
| Adverse Events (150 mg QD) | Taste perversion: 4% Diarrhea: 10% Nausea: 5% Vomiting: 2% |
| Resistance Claim | Being pursued, dependent on resistance prevalence/recovery/efficacy & availability of I.V. |



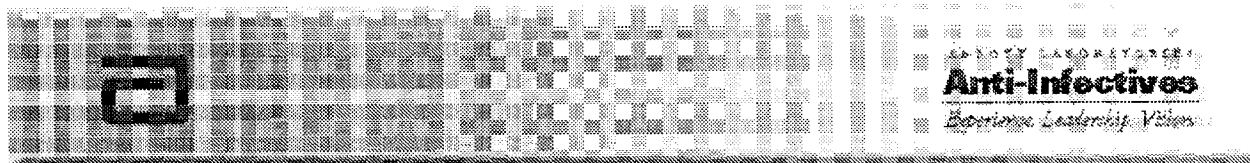
ABT-773 Profile
vs Biaxin XL

| | ABT-773 | Biaxin XL |
|------------------|-----------------------------------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------|
| Dosing | ABECB: 150 mg QD x 5 d Phar: 150 mg QD x 5 d CAP: 150 mg QD or BID x 10 d ABS: 150 mg QD or BID x 10 d | All regimens 2 x 500 mg QD ABECB: 7 d CAP: 7 d ABS: 14 d |
| Efficacy | ABECB: 87% Cure, 86% Erad ABS: 89% Cure, 77% Erad CAP: XX% Cure, XX% Phar: No data | ABECB: 83-86% Cure, 86-92% Erad ABS: 85% Cure, NA Erad CAP: 89% Cure, 89% Erad |
| Adverse Events | Taste perversion: 4% Diarrhea: 10% Nausea: 5% Vomiting: 2% | Taste perversion: 6% Diarrhea: 6% Nausea: 3% Vomiting: 1% |
| Resistance Claim | Being pursued | Under exploration |



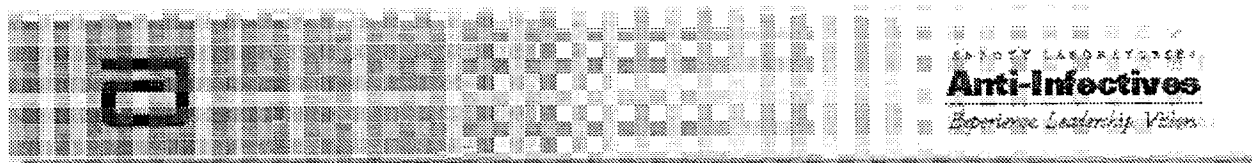
Key Commercial Challenges

- **150 mg QD vs 150 mg BID**
 - 150 mg QD may prove efficacious in CAP/ABS ==> uniform QD dosing; however, limited 150 mg QD data currently exists, hence risk of BID dosing for CAP/ABS
 - Even if 150 mg QD efficacious, this regimen could receive regulatory challenge, particularly among ex-U.S. agencies==> QD and BID development programs, increased cost
- **PK**
 - Negative implications for efficacy as well as resistance development
- **H. flu eradication**
 - dose-defining pathogen, limited number of data points to date
 - a strength of quinolones
- **Tolerability may be sub-optimal**
 - diarrhea and taste perversion
- **2nd to market ketolide**
 - Aventis ketolide Ketek (telithromycin), FDA advisory 1/29



Phase II Data: 150 mg QD vs 300 mg QD

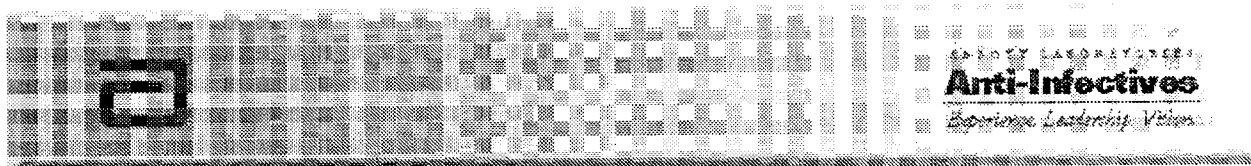
| | | | Phase IIb Data: Intent-to-treat | | | | | | | |
|----------------------|------------------|-----------|---------------------------------|---------|------|-------|-----------|-------|-------|---------|
| | | | Bronchitis | | CAP | | Sinusitis | | Total | |
| Clinical Cure | 150 mg QD | | 85% | 104/123 | | | 82% | 72/88 | 83% | 176/211 |
| | 300 mg QD | | 83% | 107/129 | 84% | 80/95 | 80% | 72/90 | 82% | 159/314 |
| Bacteriological Cure | <i>H. flu</i> | 150 mg QD | 89% | 17/19 | | | 60% | 3/5 | 83% | 20/24 |
| | | 300 mg QD | 81% | 17/21 | 100% | 9/9 | 100% | 7/7 | 89% | 33/37 |
| | <i>S. pneumo</i> | 150 mg QD | 77% | 10/13 | | | 100% | 3/3 | 81% | 13/16 |
| | | 300 mg QD | 90% | 9/10 | 82% | 14/17 | 100% | 8/8 | 89% | 31/35 |



Ketek Summary

Regulatory Status

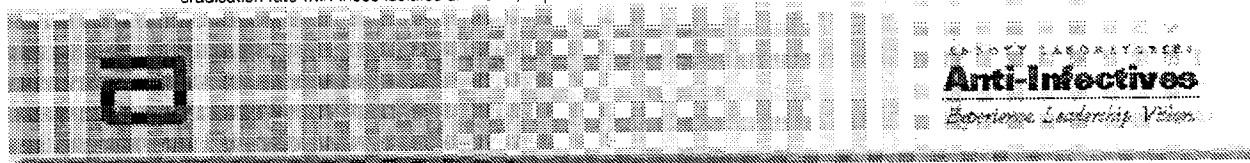
- Ketek (telithromycin, Aventis) will be first-to-market ketolide
- U.S.
 - Filed with FDA March 2000
 - **FDA advisory 1/29**
 - Expected approval 1Q01
- Ex-U.S.
 - Package submitted to EMEA as centralized filing in March 2000
 - Rapporteur = Sweden
 - Co-rapporteur = Portugal
 - Expected approval 1Q01
- Phase II in Japan (source: IMS World R&D Focus)



Ketek Summary

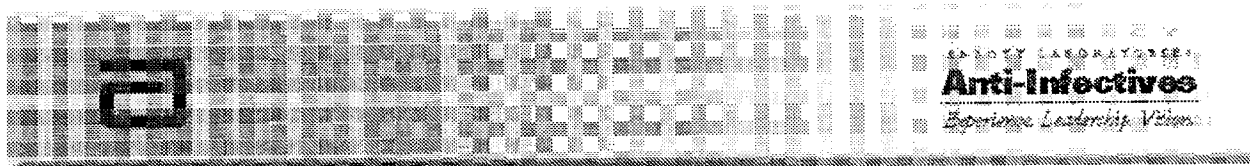
Profile Summary

-
- 800 mg QD for all indications
 - AECB (5 d), CAP (7-10d), sinusitis (5d), pharyngitis (5d)
 - High rate of diarrhea (10-20%), nausea (10%), but no taste perversion
 - statistically greater diarrhea vs trovafloxacin in phase III study
 - Comparable levels of efficacy to comparators (see appendix for full clinical summary)
 - 74%-95% clinical cure
 - 69%-94% overall eradication
 - H. flu eradication is varied, with two CAP studies having 75% and 78% eradication; an AECB and sinusitis study had H. flu eradication of 88% and 100% respectively
 - Liver function elevation
 - mentioned at ICAAC99, but Aventis claimed no clinically relevant impact at ICAAC2000; a CAP study references a 11.3% incidence of abnormal liver function, though the severity is unknown
 - QTc prolongation: Aventis maintains no clinically relevant impact
 - High COGS based on SPD pricing on intermediate
 - estimated telithromycin bulk drug cost of ~\$6,000/kg at launch vs \$3,000 for 773 at launch
 - may limit pricing flexibility
 - Competitive intelligence suggests 14 penicillin resistant isolates submitted, same number as Levaquin (potential for pen-resistance claim, which Levaquin was granted)
 - eradication rate with these isolates unknown, important factor in FDA decision



Ketek Summary
ABT-773 Comparison

| | ABT-773 | Ketek |
|------------------|-----------------------------------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------------------------------------------------------|
| Dosing | ABECB: 150 mg QD x 5 d Phar: 150 mg QD x 5 d CAP: 150 mg QD or BID x 10 d ABS: 150 mg QD or BID x 10 d | All regimens 2 x 400 mg QD ABECB: 5 d Phar: 5 d CAP: 7-10 d ABS: 10 d (or 5 d?) |
| Efficacy | ABECB: 87% Cure, 86% Erad ABS: 89% Cure, 77% Erad CAP: XX% Cure, XX% Phar: No data | ABECB: 86-89% Cure, 69-88% Erad ABS: 76-91% Cure, 86-91% Erad CAP: 91-93% Cure, 86-94% Erad Phar: 93-95% Cure, 84-91% Erad |
| Adverse Events | Taste perversion: 4% Diarrhea: 10% Nausea: 5% Vomiting: 2% | Taste perversion: Not reported Diarrhea: 10-20% Nausea: 10% Liver, QTc: ??? |
| Resistance Claim | Being pursued | Submitted in NDA |



Confidential

ABBT05120

Ketek Summary

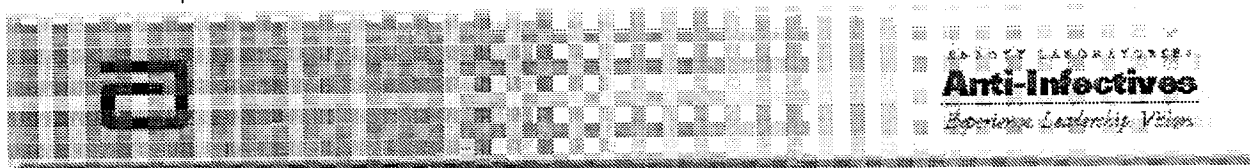
ABT-773 Strengths/Weaknesses

ABT-773 Strengths vs Ketek

- ABT-773 is considerably more potent than telithromycin against:
 - resistant and susceptible strains of *S. pneumo*
 - atypicals
 - *H. flu* (based on in vivo animal models)
- Lower rate of adverse events, particularly diarrhea
- 1 tab per dose vs 2
- Mechanistic advantages
 - faster binding to ribosome, slower release from ribosome, perhaps additional binding site(s)
- Potential for greater pricing flexibility

ABT-773 Threats/Issues vs Ketek

- 2nd to market
- Potential for BID dosing in CAP and/or sinusitis
- ABT-773 clinical/safety data at 150 mg QD based on relatively few data points
- PK profile



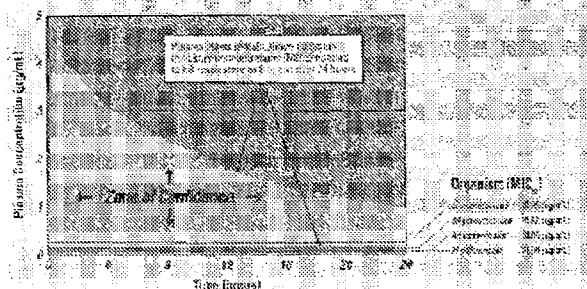
Ketek Summary Clinical Data

| | | |
|----------------|----------------------|----------------|
| ATM | 2% | 2% |
| Intermittent | 2% | 2% |
| Continuous | 2% | 2% |
| Subcutaneous | 2% | 2% |
| Pharyngitis #2 | Ketec 500 mg, 100 mg | 100 mg, 100 mg |
| Intermittent | 2% | 2% |
| Continuous | 2% | 2% |
| Subcutaneous | 2% | 2% |
| ATM #3 | Ketec 500 mg, 100 mg | 100 mg, 100 mg |
| Intermittent | 2% | 2% |
| Continuous | 2% | 2% |
| Subcutaneous | 2% | 2% |
| ATM #4 | Ketec 500 mg, 100 mg | 100 mg, 100 mg |
| Intermittent | 2% | 2% |
| Continuous | 2% | 2% |
| Subcutaneous | 2% | 2% |
| ATM #5 | Ketec 500 mg, 100 mg | 100 mg, 100 mg |
| Intermittent | 2% | 2% |
| Continuous | 2% | 2% |
| Subcutaneous | 2% | 2% |
| ATM #6 | Ketec 500 mg, 100 mg | 100 mg, 100 mg |
| Intermittent | 2% | 2% |
| Continuous | 2% | 2% |
| Subcutaneous | 2% | 2% |
| ATM #7 | Ketec 500 mg, 100 mg | 100 mg, 100 mg |
| Intermittent | 2% | 2% |
| Continuous | 2% | 2% |
| Subcutaneous | 2% | 2% |
| ATM #8 | Ketec 500 mg, 100 mg | 100 mg, 100 mg |
| Intermittent | 2% | 2% |
| Continuous | 2% | 2% |
| Subcutaneous | 2% | 2% |
| ATM #9 | Ketec 500 mg, 100 mg | 100 mg, 100 mg |
| Intermittent | 2% | 2% |
| Continuous | 2% | 2% |
| Subcutaneous | 2% | 2% |
| ATM #10 | Ketec 500 mg, 100 mg | 100 mg, 100 mg |
| Intermittent | 2% | 2% |
| Continuous | 2% | 2% |
| Subcutaneous | 2% | 2% |
| ATM #11 | Ketec 500 mg, 100 mg | 100 mg, 100 mg |
| Intermittent | 2% | 2% |
| Continuous | 2% | 2% |
| Subcutaneous | 2% | 2% |
| ATM #12 | Ketec 500 mg, 100 mg | 100 mg, 100 mg |
| Intermittent | 2% | 2% |
| Continuous | 2% | 2% |
| Subcutaneous | 2% | 2% |
| ATM #13 | Ketec 500 mg, 100 mg | 100 mg, 100 mg |
| Intermittent | 2% | 2% |
| Continuous | 2% | 2% |
| Subcutaneous | 2% | 2% |
| ATM #14 | Ketec 500 mg, 100 mg | 100 mg, 100 mg |
| Intermittent | 2% | 2% |
| Continuous | 2% | 2% |
| Subcutaneous | 2% | 2% |
| ATM #15 | Ketec 500 mg, 100 mg | 100 mg, 100 mg |
| Intermittent | 2% | 2% |
| Continuous | 2% | 2% |
| Subcutaneous | 2% | 2% |
| ATM #16 | Ketec 500 mg, 100 mg | 100 mg, 100 mg |
| Intermittent | 2% | 2% |
| Continuous | 2% | 2% |
| Subcutaneous | 2% | 2% |
| ATM #17 | Ketec 500 mg, 100 mg | 100 mg, 100 mg |
| Intermittent | 2% | 2% |
| Continuous | 2% | 2% |
| Subcutaneous | 2% | 2% |
| ATM #18 | Ketec 500 mg, 100 mg | 100 mg, 100 mg |
| Intermittent | 2% | 2% |
| Continuous | 2% | 2% |
| Subcutaneous | 2% | 2% |
| ATM #19 | Ketec 500 mg, 100 mg | 100 mg, 100 mg |
| Intermittent | 2% | 2% |
| Continuous | 2% | 2% |
| Subcutaneous | 2% | 2% |
| ATM #20 | Ketec 500 mg, 100 mg | 100 mg, 100 mg |
| Intermittent | 2% | 2% |
| Continuous | 2% | 2% |
| Subcutaneous | 2% | 2% |

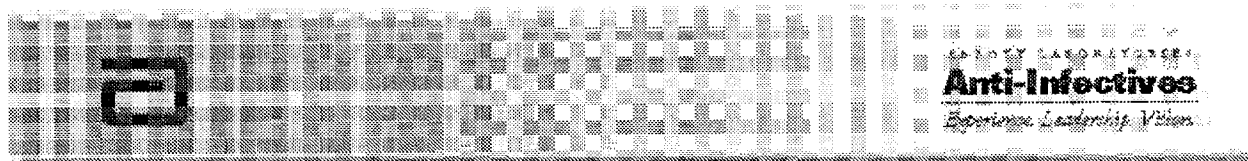
LABORATORY
Anti-Infectives
Experience. Leadership. Values.

AVELOX provides a 24-hour Zone of Confidence covering key respiratory pathogens

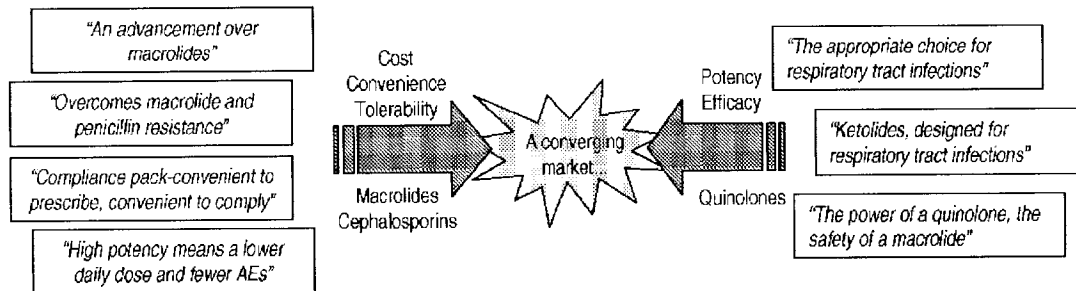
Steady-state plasma concentrations are well above MIC₉₀s of key community respiratory pathogens



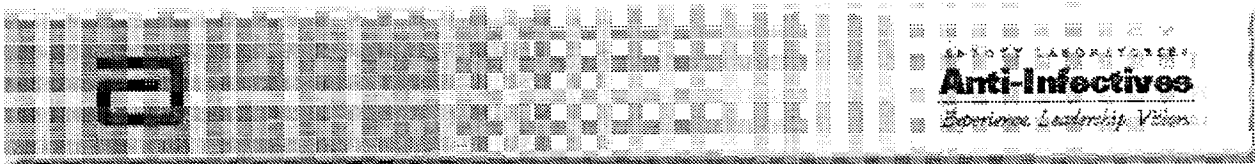
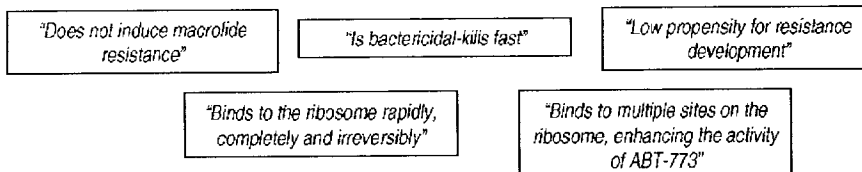
Quinolones are using PK as means of differentiating products-could increase the relevance of PK to prescribers



Key Commercial Messages

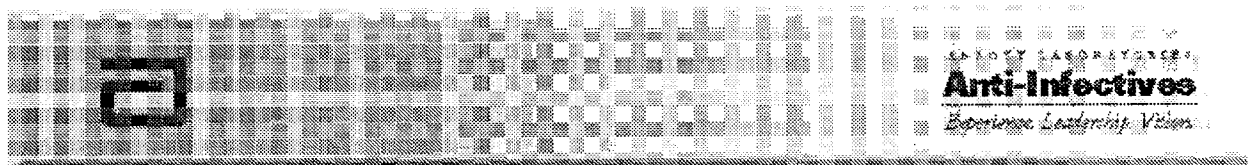


Supportive Messages



Communications Strategy

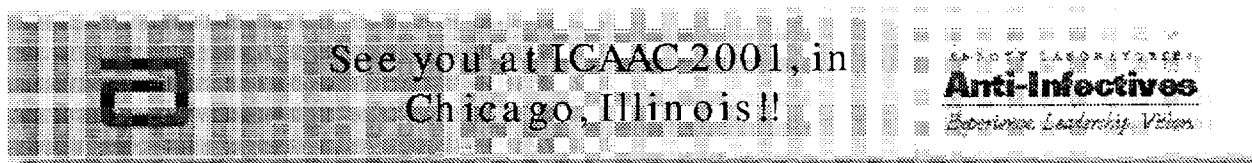
- Messages
 - microbiological data (resistance, the better ketolide)
 - PK (no food effect, favorable drug-drug)
 - Mechanism (ribosome binding, PAE, etc., “explanation” for ketolide activity, defense of dose selection)
 - Clinical data
- Implementation
 - Strategic initiation of studies to support desired messages, monthly strategy meetings, intranet under development to manage activities/history
 - Scientific meetings (51 posters at 6 scientific meetings in 1999-2000)
 - Publications (10 publications in 2000)
 - Medical Liaisons(sp)
 - VIP Visits



PART 7

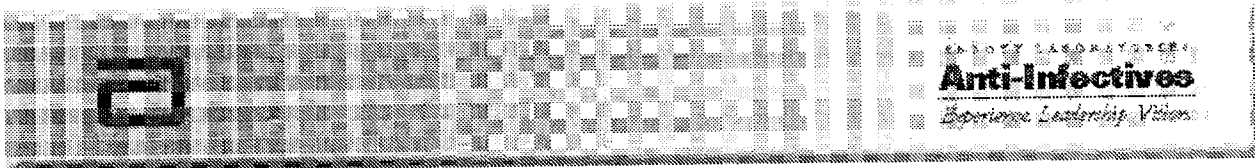
ICAAC 2000

International Conference on Antimicrobial Agents and Chemotherapy, Toronto



Forecast Assumptions

| | <u>US</u> | <u>Europe</u> | <u>Japan</u> |
|----------|-------------------------------------------------------------------------|---------------|--------------|
| Dosing | 150 mg QD dosing all indications AECB & Phar, 5 d CAP & ABS, 10 d | | |
| Efficacy | Comparable to other agents | | |
| AEs | Comparable to Biaxin XL | | |
| COGS | \$3,000/kg at launch | | |
| AWP/Day | \$8.60 | | |

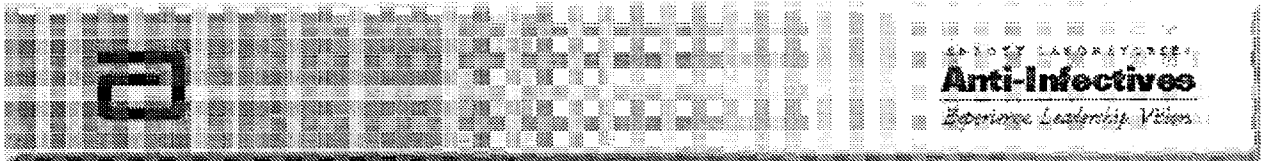


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ABRT205127

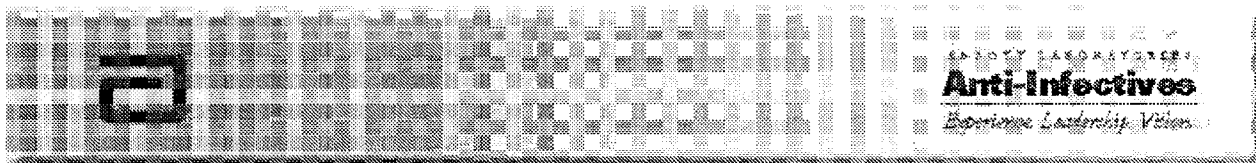
Forecast

| | <u>U.S.</u> | <u>Europe</u> | <u>Japan</u> | <u>ROW</u> | <u>Total</u> |
|----------------|-------------|---------------|--------------|------------|--------------|
| Peak Sales | \$432MM | | | | |
| Peak TRX Share | 7.5% | | | | N/A |
| NPV @12.5% | | | | | |

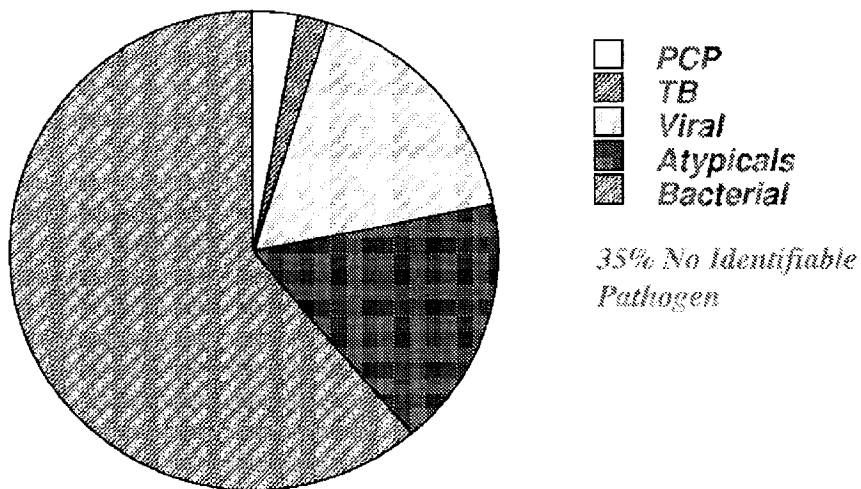


Microbiology ***Overview***

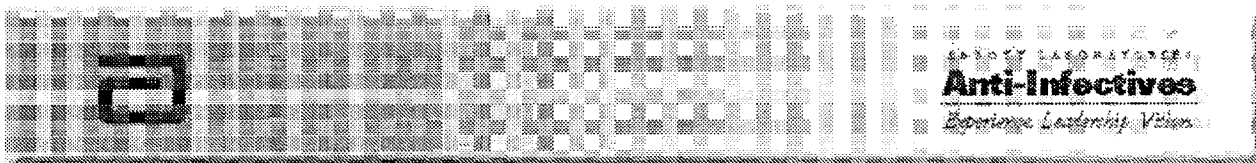
- **Ketolides are a Novel Class of Antimicrobial**
 - Active vs. key respiratory tract infection pathogens to include macrolide resistant streptococci
 - Bactericidal activity
 - Prolonged post antibiotic effect
 - Reduced resistance development



Microbiology
Community-Acquired Pneumonia in Adults

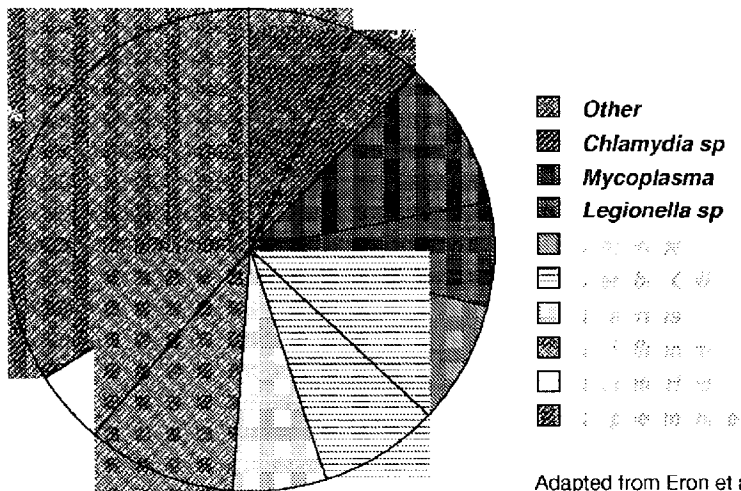


Adapted from Eron et al. Hosp Form 1994;29:122

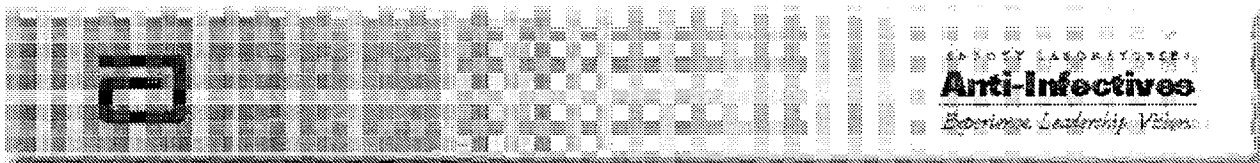


Microbiology

Bacterial Causes of Community-Acquired Pneumonia in Adults

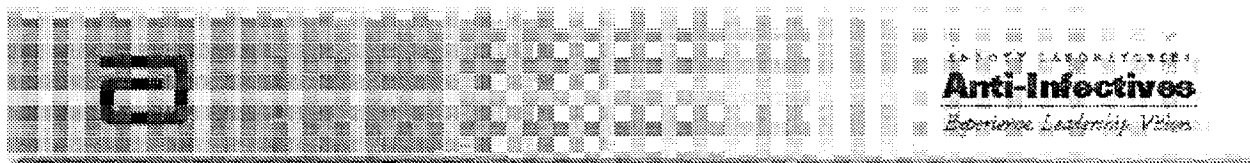
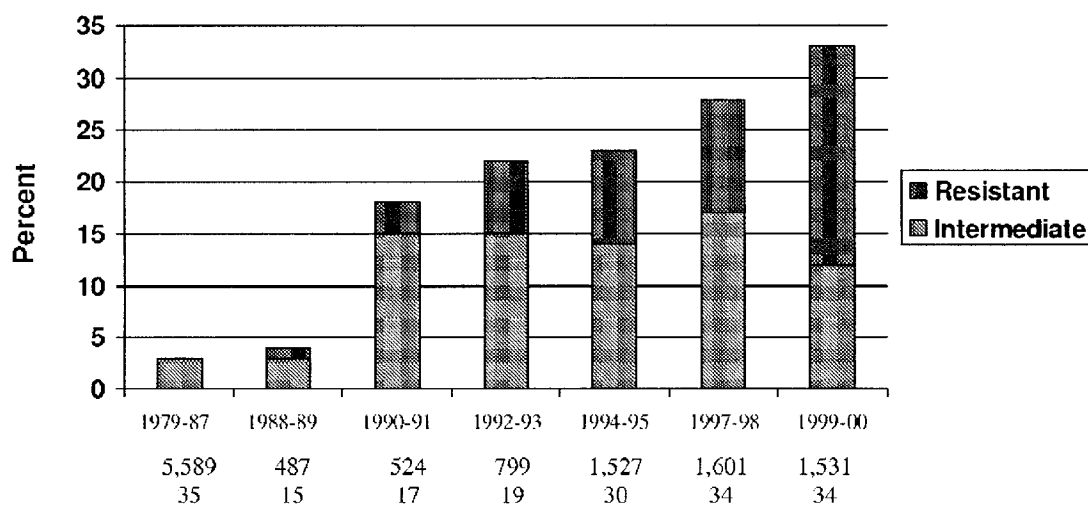


Adapted from Eron et al. Hosp Form 1994;29:122



Microbiology

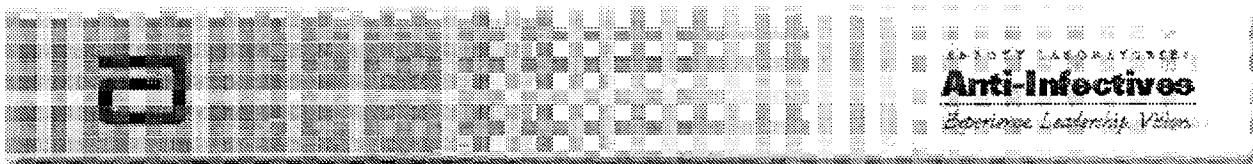
Penicillin resistance with *Streptococcus pneumoniae* in the United States



Microbiology***US Respiratory Surveillance Studies, Penicillin Susceptibility in *S. pneumoniae****

| <i>Year</i> | <i>1994-95</i> | <i>1997-98</i> | <i>1999/2000</i> |
|---------------------------|-------------------|-------------------|-------------------|
| Season | Winter | Winter | Winter |
| No. of centers | 30 | 34 | 34 |
| No. of isolates | 1,528 | 1,601 | 1531 |
| No. % intermediate | 216 (14.1) | 278 (17.4) | 194(12.7%) |
| No. % resistant | 145 (9.6) | 196 (12.2) | 29 (21.5%) |

Dr. G. Doern, Univ. of Iowa



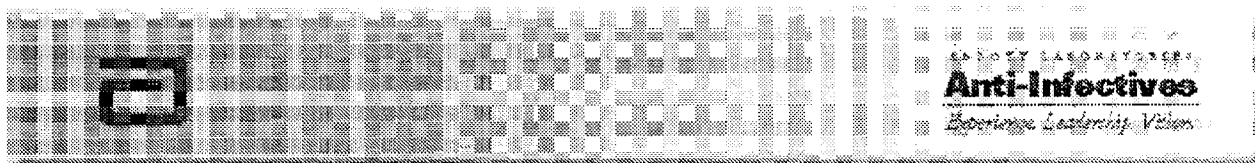
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ABBT205133

Microbiology
Antimicrobial Resistance Rates among *S. pneumoniae*

| | 1994-95 | 1997-98 | 1999-2000 |
|---------------------|---------|---------|-----------|
| Antimicrobial Agent | N=1527 | N=1601 | N=1531 |
| Macrolide | 10.0 | 18.9 | 25.9 |
| Tetracycline | 7.5 | 12.9 | 16.4 |
| Chloramphenicol | 4.3 | 7.2 | 8.4 |
| Clindamycin | Na | 5.6 | 8.8 |
| TMP/SMX | 18.0 | 20.4 | 30.3 |

Dr. G. Doern, Univ. of Iowa



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ABBT05134

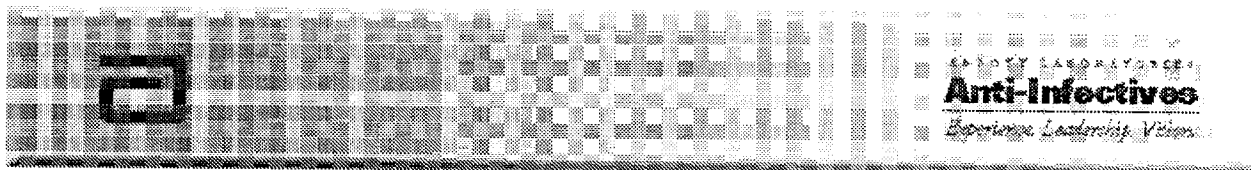
Microbiology

*Rates of Resistance of Non- β -Lactam Antimicrobials with Streptococcus pneumoniae
Based on Penicillin Susceptibility Category*

Percentage Resistance Among

| <u>Antimicrobial</u> | <u>PenS-(n=1,008)</u> | <u>PenI(n=194)</u> | <u>PenR(n=1,531)</u> |
|----------------------|-----------------------|--------------------|----------------------|
| Macrolides | 5.6 | 43.3 | 78.1 |
| Clindamycin | 1.4 | 19.1 | 25.2 |
| Chloramphenicol | 1.0 | 13.9 | 27.7 |
| Tetracycline | 3.1 | 32.0 | 48.0 |
| TMP/SMX | 7.6 | 39.2 | 94.5 |

[n=1,531, 34 U.S. centers, 1999-2000], Doern et al

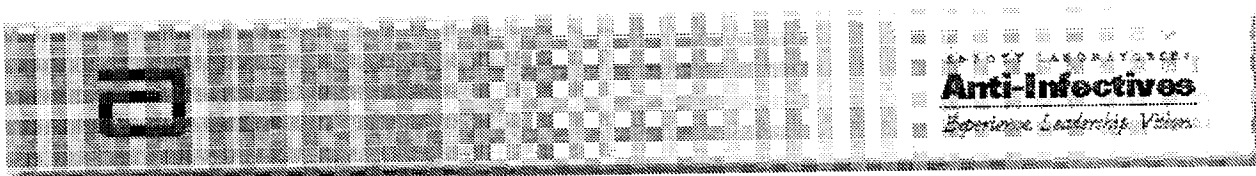


Microbiology
Macrolide Resistance Types

Microbiology Overview

• **Two major macrolide resistance mechanisms in streptococci and staphylococci:**

- Ribosomal methylase – blocks macrolide binding to target
 - Macrolide and clindamycin MIC $>16 \mu\text{g/mL}$
- Macrolide efflux – actively pumps macrolide out of cell
 - Macrolide MIC $1\text{--}32 \mu\text{g/mL}$; clindamycin MIC $\leq 0.25 \mu\text{g/mL}$



Microbiology

Resistance Mechanisms Prevalence in *S. pneumoniae* Clinical Isolates

| Genotype | U.S. 1994-95 ¹ n=114 | U.S. 1997-98 ² n=302 | Canada ³ n=147 | Europe ⁴ n=21 | Japan ⁵ n=62 |
|-----------------------|---------------------------------------|---------------------------------------|------------------------------|-----------------------------|----------------------------|
| <i>ermB</i> | 32% | 29% | 39% | 97% | 40% |
| <i>mefE</i> | 61% | 71% | 56% | 3% | 43% |
| <i>mef/erm</i> | 5% | — | <1% | - | 16% |
| Unknown | 2% | — | 6% | - | 0% |

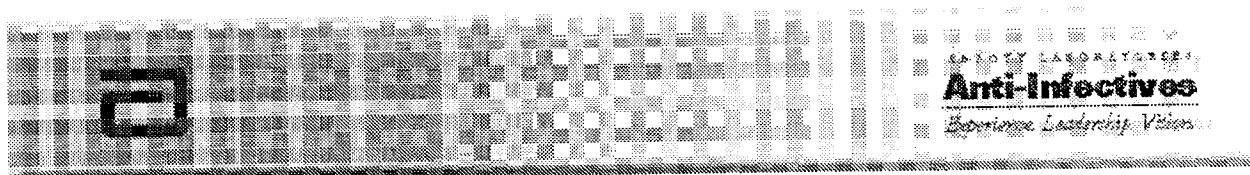
¹Shortridge, et al. *CID*. 1999; 29:1186-8.

²Doern, et al. *EID*. 1999; 5(6).

³Johnston, et al. *AAC*. 1998; 42:2425-26.

⁴Schmitz et. al. *JAC*. 1999.43:783-92

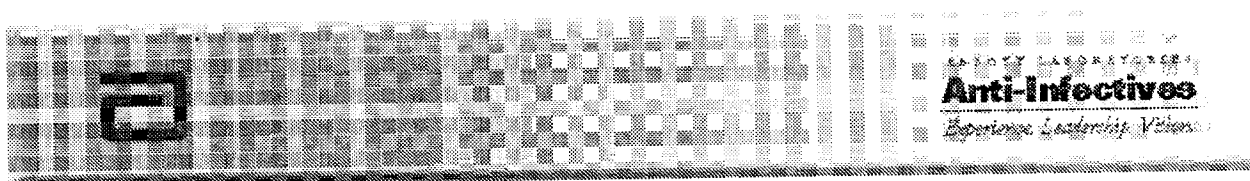
⁵Nishijima et. al. *JAC*. 1999.43:637-643



Microbiology**ABT-773 Activity, University of Iowa Resistance Survey****Isolates by Erythromycin MIC**

| Drug | Erythromycin MIC $\leq 0.5 \mu\text{g/ml}$ (n=1299) | | Erythromycin MIC 1-32 $\mu\text{g/ml}$ (n=222) | | Erythromycin MIC $\geq 64 \mu\text{g/ml}$ (n=80) | |
|---------|-----------------------------------------------------------|---------------------|------------------------------------------------------|--------------------|--------------------------------------------------------|--------------------|
| | MIC ₉₀ | MIC range | MIC ₉₀ | MIC range | MIC ₉₀ | MIC range |
| ABT-773 | ≤ 0.008 | $\leq 0.008 - 0.12$ | 0.03 | $\leq 0.008 - 0.5$ | 0.12 | $\leq 0.008 - 0.5$ |

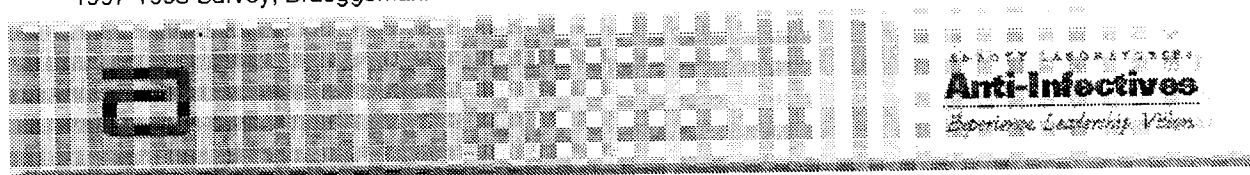
1997-1998 Survey, Brueggemann et. al.2000. AAC. 44:447-449



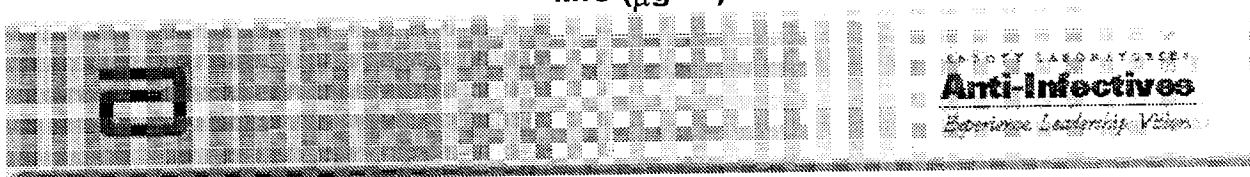
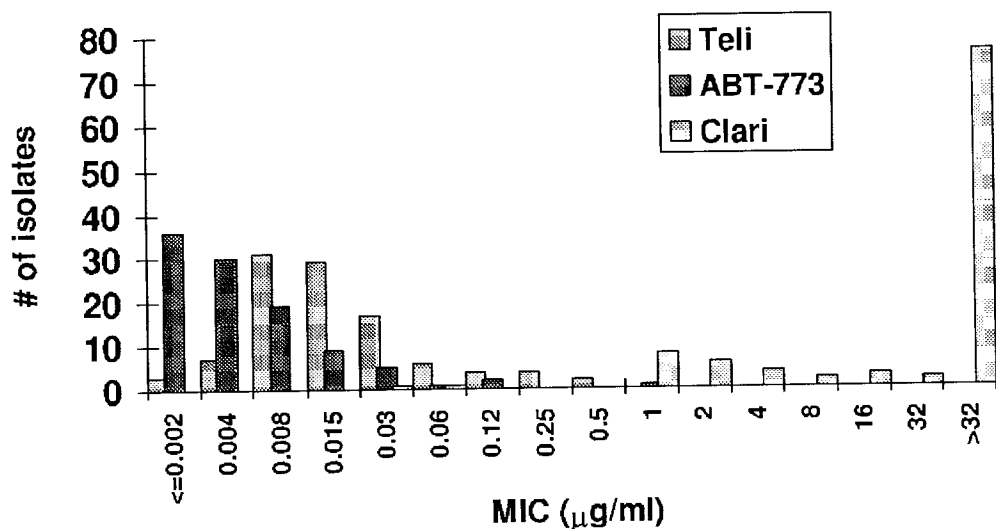
Microbiology**ABT-773 Activity, University of Iowa Resistance Survey****Isolates by Penicillin MIC**

| Drug | Penicillin Susceptible MIC ≤ 0.06 $\mu\text{g/ml}$ (n=1127) | | Penicillin Intermediate MIC 0.12-1.0 $\mu\text{g/ml}$ (n=278) | | Penicillin Resistant MIC ≥ 2.0 $\mu\text{g/ml}$ (n=196) | |
|---------|------------------------------------------------------------------------|--------------------|---------------------------------------------------------------------|--------------------|--------------------------------------------------------------------|---------------------|
| | MIC ₉₀ | MIC range | MIC ₉₀ | MIC range | MIC ₉₀ | MIC range |
| ABT-773 | ≤ 0.008 | $\leq 0.008 - 0.5$ | 0.03 | $\leq 0.008 - 0.5$ | 0.12 | $\leq 0.008 - 0.25$ |
| Ery | 0.06 | $\leq 0.03 - >64$ | >64 | $\leq 0.03 - >64$ | >64 | $\leq 0.03 - >64$ |

1997-1998 Survey, Brueggemann et. al. 2000. AAC. 44:447-449

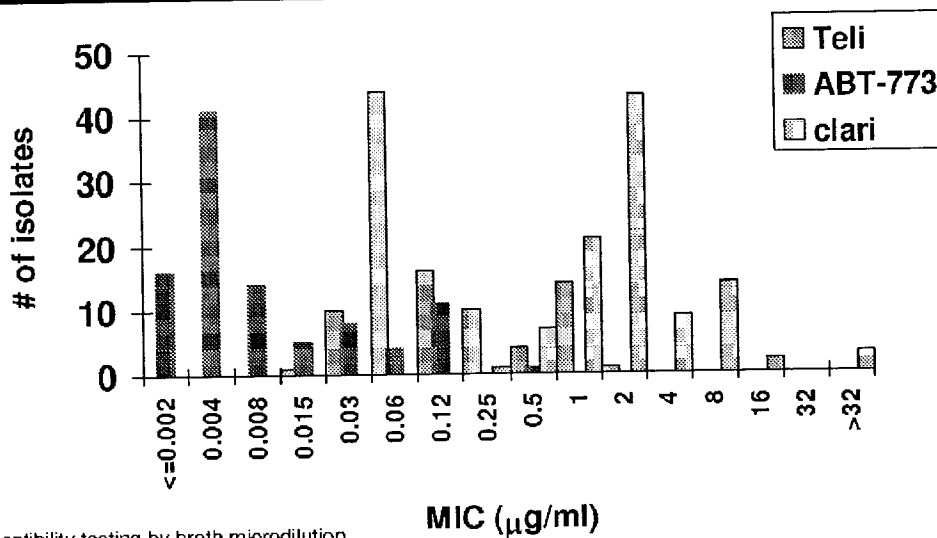


Microbiology
MIC Distribution of *S. pneumoniae* methylase⁺ strains

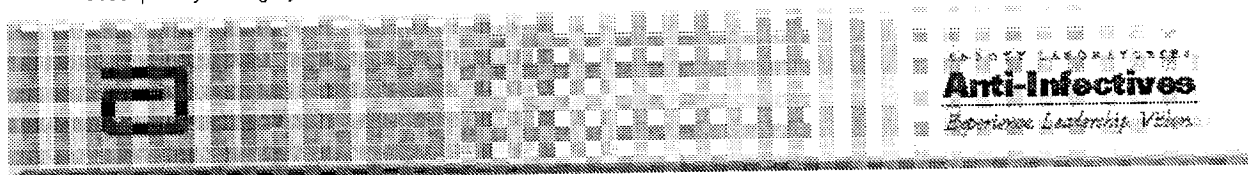


Microbiology

MIC Distribution of S. pneumoniae efflux⁺ strains



Susceptibility testing by broth microdilution



Microbiology
In vitro Activity, S. pyogenes

MIC₉₀ Range in µg/ml

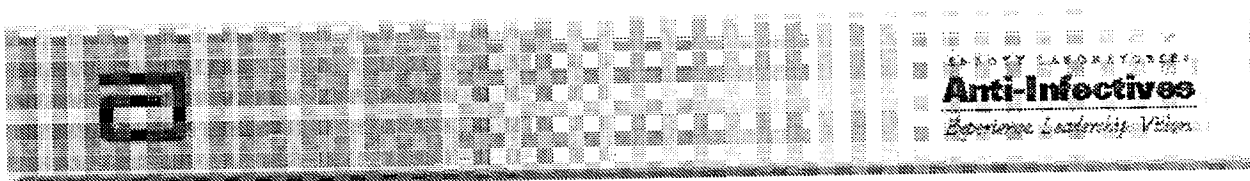
| Organism | Macrolide susceptible | Macrolide resistant |
|--------------|-----------------------|---------------------|
| ABT-773 | ≤0.016 - 0.03 | 0.06 - 0.12 |
| Erythromycin | 0.06 - 0.12 | 8 - 16 |

References:

Barry et al ICAAC 1999 #2144

Dubois et al. ICMASKO 2000 #2.15

Singh et al. ICMASKO 2000 #2.14



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ABBT205143

Microbiology*In vitro Activity, Haemophilus, Moraxella spp.***MIC₉₀ Range in µg/ml**

| Organism | <i>H. influenzae</i> | <i>M. catarrhalis</i> |
|--------------|----------------------|-----------------------|
| ABT-773 | 2 - 4 | 0.06 - 0.25 |
| Azithromycin | 2 - 4 | 0.06 - 0.12 |
| Erythromycin | 8 - 16 | 0.25 - 0.5 |

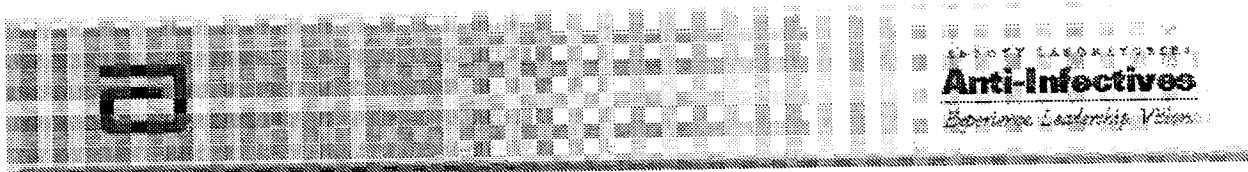
References:

Barry et al ICAAC 1999 #2144

Hoellman et al ICAAC 1999 #2140

Brueggemann et al. 2000.AAC.44:447-449

Shortridge et. al.1999. ICAAC



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ABBT205144

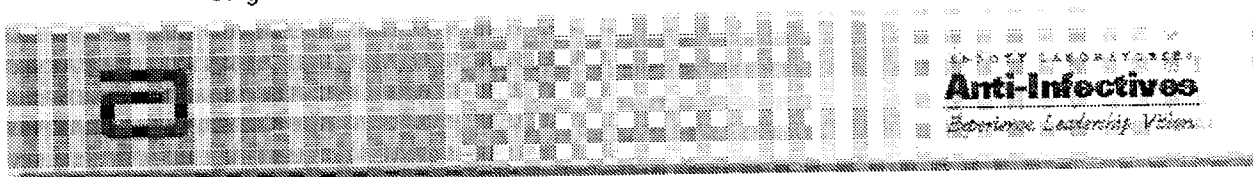
Microbiology**Comparison of activity vs. respiratory atypical pathogens**MIC₉₀ in µg/ml

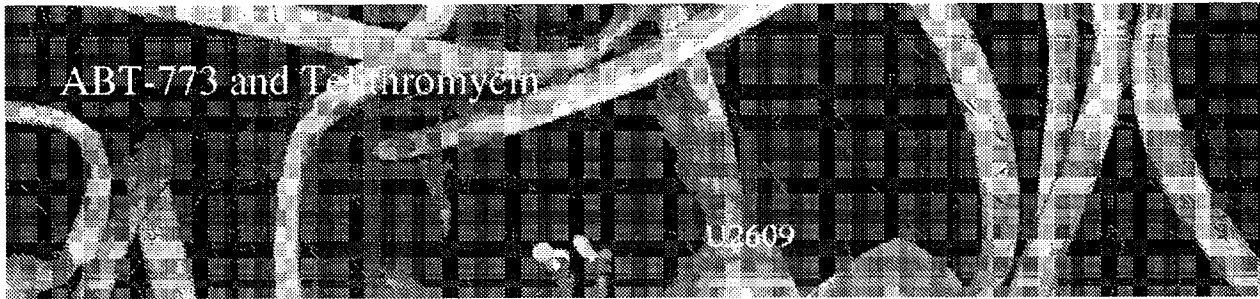
| Organism | ABT-773 | Ery |
|-------------------------------------------|-----------|----------|
| <i>Legionella</i> spp. ¹ (105) | 0.03-0.12 | 0.25-1.0 |
| <i>M. pneumoniae</i> ² (18) | ≤ 0.0005 | 0.008 |
| <i>C. pneumoniae</i> ³ (20) | 0.015 | 0.06 |

¹Victor Yu, ICAAC, 2000. Strains tested: *L. pneumophila* serogroup 1 (68), *L. pneumophila* other serogroups (28), *Legionella* spp other than pneumophila (10).

².Nilius et al. ECCMID 1999.

³ Strigl et. al.2000. AAC.44:1112-1113





PENGAD 800-631-6989

Mar-01

| | |
|-------------------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Next GenNo Go Business | Receipt of Phase III data 2001 dose selection for CAP & singalis |
| .. Rationale | AB1773 represents a key product for the global anti-infective franchise given the patent expiration of clindamycin 2004-2005 The product has a compelling selling proposition by virtue of its novel lantidide class, its activity against resistant organisms, and potential tolerability/safety advantages relative to the Aventis lantidase Kestrel |

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ABBT 0000429

March 2001**ABT-773****Monthly Highlights – Key Project Progress**

- With the ending of the winter season, Phase III enrollment for CAP (189 actual) and sinusitis (253 actual) are behind projections. Ethics committee approvals in Europe are continuing, 178 (U.S. and EU) CAP sites now have drug and 66 EU site approvals are in process. For sinusitis, 84 (US and EU) sites have drug and 50 EU site approvals are in process.
- Further Phase III start up activities are ongoing in Central America, So Africa and So America for CAP and ABS for their winter seasons starting in May. As we proceed with the enrollment in the Northern Hemisphere during April, we will make a final decision on initiating these sites for enrollment to be as cost effective as possible.
- A strategy to address European and US requirements regarding QT intervals is being formulated and will be finalized in April.
- The initial Phase I study for the IV formulation is on target to start in early May. This study will enable us to evaluate the appropriate IV dose and evaluate injection site pain with the formulation prior to a Multiple Dose study. Timing for Phase I Go/No Go is planned for September.
- The CMC and Biopharm End of Phase II meeting targeted for end of April was delayed by FDA to May 1st due to the FDA advisory for Ketek at the end of April.
- The Japanese development strategy is currently being re-addressed in light of organizational changes and the status of CAP and Sinusitis dose selection decision.

Next Quarter's Key Progress Markers

| Key Progress Marker | Target Date |
|---------------------------------------------------------------------------------------------------------------------------------------------------------|-------------|
| Hold CMC/Biopharm End of Phase II meeting with FDA. | 05/31 |
| Determine if Southern Hemisphere sites for CAP and ABS should be initiated as a contingency if US/European enrollment fails to meet 500 patient target. | 04/30 |
| Complete enrollment in CAP and ABS Dose selection studies to meet Dose Decision milestone in July, assuming US/Europe can meet 500 patient target. | 06/01 |
| Complete enrollment in ASP and ABECB comparator studies in the U.S. | 06/01 |
| Complete intermediate scale-up activities in the U.K. site for initial bioequivalence study between Abbott Park and U.K. mfg sites. | 05/31 |
| Initiate first Phase I study of IV formulation. | 05/01 |
| Results available for Japan Phase I Dose Ranging study to determine Japan dose for Phase II/III studies and potential Bridging strategy. | 04/15 |

Key Project Issues and Risks

| Risk or Issue | Potential or Known Impact Check all that apply and Describe Impact | Strategy/Progress | Area / Responsibility | Resolution Date Planned / Actual |
|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----------------------|-------------------------------------|
| Clinical enrollment challenges due to a) delay in end of phase II meeting from September to November at request of FDA b) delay in start of study due to protocol changes requested by FDA c) light 2000-01 flu/respiratory season | <input checked="" type="checkbox"/> Cost <input checked="" type="checkbox"/> Time <input type="checkbox"/> Profile <input checked="" type="checkbox"/> Regulatory Critical path trials to development timeline are CAP & sinusitis, with dose decision for these indications needed by 7/2001 to maintain current timeline. Actual enrollment is lagging predictions. | A decision to initiate the Southern Hemisphere sites will be made in April as a contingency should the US and Europe fail to meet enrollment targets for CAP and sinusitis. ASP and ABECB studies are not on the critical path. | Venture | 7/2001 |

2 of 10

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ABT 0000430**

March 2001

ABT-773

Key Project Issues and Risks

| Risk or Issue | Potential or Known Impact Check all that apply and Describe Impact <input type="checkbox"/> Cost <input checked="" type="checkbox"/> Time <input checked="" type="checkbox"/> Profile <input checked="" type="checkbox"/> Regulatory | Strategy / Progress | Area / Responsibility | Resolution Date Planned / Actual |
|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----------------------|-------------------------------------|
| 150 mg QD vs BID dose decision in CAP/sinusitis. | <input checked="" type="checkbox"/> Cost <input checked="" type="checkbox"/> Time <input checked="" type="checkbox"/> Profile <input checked="" type="checkbox"/> Regulatory Current AI opinion is that QD may receive regulatory challenge for approval in CAP unless data is very compelling given PK profile of 150 mg QD; however, BID dosing, while relatively minor commercial impact ex-US, represents significant commercial hurdle in US. | Decision must be made in light of QD vs BID CAP and sinusitis data (7/2001); DSG analysis is planned to facilitate decision; internal efforts to defend 150 mg QD dosing with data on potent ribosome binding properties of ABT-773 are ongoing by Discovery, with an advisory planned with external experts Aug 2001 to define further study. | Venture/NPD/DSG | 7/2001 |
| Regulatory uncertainties over how to deal with the ketolide/macrolide class regarding QT interval effects. | <input type="checkbox"/> Cost <input type="checkbox"/> Time <input checked="" type="checkbox"/> Profile <input checked="" type="checkbox"/> Regulatory Additional studies could be required to show no effects on QT. Class labeling could negatively impact sales of the product. | FDA requested an acute tox study in dog to further evaluate cardiac effects and also discussed whether a Phase I study should be conducted in subjects with underlying cardiac disease. A QT strategy is under development to be finalized in April. | Regulatory | 6/2002 |
| Definition of starting materials for the bulk drug (at what step in the manufacturing process) will affect our ability to continue with process improvements necessary to continue to reduce the cost of the bulk drug. This has cost implications up to 3 years post-launch. | <input checked="" type="checkbox"/> Cost <input type="checkbox"/> Time <input type="checkbox"/> Profile <input type="checkbox"/> Regulatory Ability to define step 5 as the starting material will allow us to make further process improvements to reduce the cost of the bulk drug. | The end of Phase II package outlining our plans for starting materials was submitted to FDA on March 1. Meeting date has been postponed by FDA due to FDA advisory planned for Ketek at the end of April. New meeting date is May 1. | SPD | 04/2001 |
| The pharmacokinetic profile of QD dose could receive regulatory challenge or be viewed as sub-optimal commercially, particularly with respect to <i>H. influenzae</i> . | <input type="checkbox"/> Cost <input type="checkbox"/> Time <input checked="" type="checkbox"/> Profile <input checked="" type="checkbox"/> Regulatory Support by PK/DPD experts is important for positioning this product in the marketplace. Competitors may challenge ABT 773 efficacy without expert support for the efficacy model. | PK/DPD data together with ribosome kinetics support the decision to proceed with 150mg QD in mild infections (ABECB and ASP) and select between 150mg BID and 150mg QD in CAP and ABS. Recent PK/DPD data support AUC of 1-6 for clinical exposure in CAP necessary for cure. Dose decision for CAP & sinusitis expected 7/2001. To address this issue and potentially create a new model for evaluating PK/DPD, internal efforts to characterize ribosome binding properties are ongoing by Discovery, with an advisory planned with external experts Aug 2001 to define further study. | Venture/NPD | 07/2001 |

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March 2001

ABT-773

Key Project Issues and Risks

| Risk or Issue | Potential or Known Impact Check all that apply and Describe Impact <input type="checkbox"/> Cost <input type="checkbox"/> Time <input checked="" type="checkbox"/> Profile <input type="checkbox"/> Regulatory Without a sufficient number of isolates, we will not obtain a claim based on clinical results for activity against resistant pathogens. Will need to rely on in vitro data only to support this claim. | Strategy / Progress | Area / Responsibility | Resolution Date Planned / Actual |
|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----------------------|-------------------------------------|
| Obtain sufficient quantity of clinical isolates with resistant organisms to request a separate claim for activity against resistant <i>S. pneumoniae</i> . | | FDA feedback regarding a resistance claim for PRSP is that a sufficient "body of evidence" needs to be gathered to convince them to grant a claim. They estimate >10 resistance isolates will be required, CAP and ABECB isolate requirements need further clarification, but ABS isolates are evaluated separately. They are not convinced about the clinical significance of MRSP and need further evidence. They suggest that an IV formulation to obtain bacteremic patients and more severe CAP infections will enhance the probability of obtaining the claim. The Phase I study to evaluate the IV formulation prototype will initiate in May 2001. | Venture | 06/2002 |
| Due to the dose change in the base development program, Phase I was repeated in Japan to further evaluate dose-ranging. A Japanese dose and formulation, as well as the Phase II/III studies, will be defined once the dose-ranging has been completed. This plan will determine the filing date for Japan. | <input checked="" type="checkbox"/> Cost <input checked="" type="checkbox"/> Time <input type="checkbox"/> Profile <input checked="" type="checkbox"/> Regulatory | The Japan Phase I Dose-Ranging study was completed in February and drug analysis is ongoing. Phase I results and Dose selection decision are needed prior to a Kiko meeting to discuss the Phase II/III strategy. The Japanese development strategy will be re-evaluated in light of the organizational changes and dose selection decision timeframe. | Japan | 08/2001/ |
| The initial development of an IV formulation has been completed and clinical supplies have been manufactured by HPD. Full development of the IV formulation has not been committed. | <input checked="" type="checkbox"/> Cost <input type="checkbox"/> Time <input type="checkbox"/> Profile <input type="checkbox"/> Regulatory Phase I will proceed to a Go/No Go decision based on initial milestone funding. | The single rising dose Phase I studies for the IV has been funded to enable us to evaluate the viability of the formulation in terms of pain on injection and the dose requirements. It will start on May 21st. A Go/No go decision on the IV formulation is planned for Sept. 2001. | HPD, Venture | 09/2001 |

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March 2001**ABT-773****Key Activities**

| Commercial | | LBE | Actual |
|----------------------------------------------------------|--|------|------------------------|
| Activity | | | |
| Completion of study tracking intranet | | 2001 | |
| Integration of intranet into communication plan | | 2001 | |
| Integration of intranet into draft product label | | 2001 | |
| Identification of communication vendor | | 2001 | |
| Submission of brand/USAN names | | 2001 | USAN submitted 3/01 |
| Preliminary qualitative positioning research | | 4Q01 | |
| Quantitative market research to support revised forecast | | 4Q01 | |
| Preliminary qualitative positioning research | | 4Q01 | |

| Formulation | | Plan | Actual |
|------------------------------------------|--|---------|---------|
| Activity | | | |
| Phase I Formulation (Caps)* | | 12/1997 | 12/1997 |
| Phase II Formulation (Tablet) | | 7/1999 | 8/1999 |
| Clinical Supplies Phase IIB | | 7/1999 | 8/1999 |
| Phase III Formulation (Tablet) | | 4/2000 | 7/2000 |
| Phase III Clinical Supplies Manufactured | | 9/2000 | 9/2000 |
| NDA Lots (3) Completed | | 7/2000 | 01/2001 |
| Completion of 1 Year Stability for NDA | | 8/2001 | |
| Formulation Peer Review | | 11/2001 | |

| Drug Substance | | KG | Plan | Actual | Plan Date: | Actual Projected Cost/kg |
|----------------|--|----|------|--------|------------|--------------------------|
| Activity | | | | | | |

| Toxicology | | Plan Start 7/1997 | Actual Start Date | Report Completed | Plan Date: 12/98 |
|------------------------------|--|----------------------|----------------------|---------------------|------------------|
| Toxicology Activity | | | | | |
| 2-week oral Rat/Monkey | | 7/1997 | 6/1997 | 9/1998 | |
| Acute Studies | | 8/1997 | 8/1997 | 12/1997 | |
| Mouse Lymphoma/Micronucleus | | 11/1997 | 11/1997 | 4/1998 | |
| 1 Month Rat/Monkey | | 12/1997 | 12/1997 | 12/1998 | |
| Pregnant Rat/Rabbit RF | | 1/1998 | 1/1998 | 11/1998 | |
| SEG II Rat/Rabbit | | 3/1998 | 3/1998 | 2/1999 | |
| Guinea pig sensitization | | 11/1998 | 11/1998 | 2/1999 | |
| 3 Month oral Rat/Monkey | | 9/1999 | 10/8/1999 | 8/2000 | |
| Seg I/II Rat | | 9/1999 | 10/8/1999 | 12/2000 | |
| IV Initiation studies, set 1 | | 7/1999 | 7/15/1999 | 8/1999 | |
| IV Initiation studies, set 2 | | 2/2000 | 2/2000 | 3/2000 | |
| IV 2-week Rat/Monkey Studies | | 6/2000 | 6/2000 | 01/2001 | |
| Neonatal/Juvenile Rat | | 10/1999 | 11/1999 | 7/2000 | |

See the Following page for a
summary of Bulk Drug
deliveries in SPD.

* Target cost of drug substance at launch is \$2,500/kg (Finished Product)

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March 2001

ABT-773

| SPD ABT-773 Bulk Drug Deliveries Update | | | | | | |
|-----------------------------------------|-------------|--------|---------------|-------------------|--------------|----------------------|
| | Target Date | Amount | Delivery Date | Amount | Lot # | Amount after milling |
| Campaign 1 | 2/28/99 | 200 Kg | 2/23/99 | 209 Kg | 50-007-CA-00 | 207.5 Kg (2/26)* |
| Campaign 2a | 6/15/99 | 140 Kg | 6/17/99 | 131 Kg | 54-702-NI-00 | 129.4 Kg (6/19)* |
| Campaign 2b | 7/15/99 | 140 Kg | 7/21/99 | 121.5 Kg | 55-208-CB-00 | 119.3 Kg (8/4)* |
| Tox lot | 8/30/99 | 5 Kg | 8/25/99 | 6.1 Kg | 55-718-NI-00 | |
| Campaign 3a | 9/30/99 | 160 Kg | 10/8/99 | 170.5 Kg | 58493CB00 | 138.4 Kg (10/16)* |
| Campaign 3b | 10/21/99 | 160 Kg | 10/11/99 | 176.5 Kg | 58494CB00 | 169.5 Kg (10/16)* |
| Pilot run 1 | ***** | 15 Kg | 10/30/99 | 18.9 Kg | 59763NI00 | no milling |
| Pilot run 2 | ***** | 15 Kg | 2/5/00 | 15.5 Kg | 61790NI00 | no milling |
| Pilot run 3 | ***** | 25 Kg | 1/30/00 | 27.5 Kg | 62764CB00 | 27.3 Kg (4/18)* |
| Campaign 4 | 12/10/99 | 320 Kg | 11/23/99 | 355 Kg | 61741CB00 | 309 Kg (3/2)* |
| Campaign 5 | 12/30/99 | 300 Kg | 12/16/99 | 300.5 Kg | 60665CB00 | 269.2 Kg (3/3)* |
| Campaign 6 | 2/28/00 | 280 Kg | 2/23/00 | 321 Kg | 62796CB00 | 315.5 Kg (3/6)* |
| Campaign 6 (IV) | 2/28/00 | 15 Kg | 2/22/00 | 20 Kg | 62797CB00 | 18 Kg (3/15)* |
| Campaign 7 | 3/30/00 | 300 Kg | 4/10/00 | 370 Kg | 63890CB00 | 361.2 Kg (4/18)* |
| Campaign 7 (IV) | 3/30/00 | 5 Kg | 3/29/00 | 19 Kg | 63889CB00 | 17.2 Kg (4/11)* |
| Campaign 8 | 4/25/00 | 200 Kg | 5/11/00 | 263 Kg | 64970CB00 | 256.5 Kg (5/15) |
| Campaign 8 (IV) | 4/25/00 | 15 Kg | 4/25/00 | 19.8 Kg | 64971CB00 | 17.7 Kg (5/11)* |
| Campaign 9 | 6/15/00 | 300 Kg | 6/14/00 | 375.7 Kg | 65064CB00 | 355.7 Kg (6/20/00) |
| Campaign 9 (IV) | 6/15/00 | 15 Kg | 6/5/00 | 18.1 Kg | 65065CB00 | 16.7 Kg (6/9/00)* |
| Campaign 10 | 7/15/00 | 300 Kg | 7/26/00 | 361.2 Kg | 67176CB00 | 359.0 Kg (8/10/00) |
| Campaign 11 | 8/15/00 | 300 Kg | 8/4/00 | 333.7 Kg | 68285CB00 | 271.9 Kg (9/7/00) |
| Campaign 12 | 10/6/00 | 300 Kg | 9/27/00 | 356 Kg | 69458CB00 | 292.3 Kg (12/8/00) |
| Campaign 13 | 11/23/00 | 300 Kg | 11/15/00 | 351.2 Kg | 71665CB00 | 349.1 Kg (12/20/00) |
| | | | | Total (year 2000) | 2,815.5 Kg | |
| Campaign 14 | 1/28/01 | 300 Kg | 1/26/01 | 327.5 Kg | 73886CB00 | 318.9 Kg (02/13/01) |
| Campaign 15 | 2/10/01 | 330 Kg | 1/14/01 | 354.9 Kg | 71699CB00 | 353.8 Kg (02/02/01) |
| * Weight after rework | | | | | | |

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ABBT 0000434

March 2001

ABT-773

All Clinical Studies:

| Protocol Number | Phase | Study Name | Start 1 st Pt. Dosed | End (Last CRF In) | Patients | | Protocol Number | Phase | Study Name | Start 1 st Pt. Dosed | End (Last CRF In) | Patients | |
|-----------------|-------|-------------------------------------|---------------------------------|-------------------|----------|---------|-----------------|-------|------------|---------------------------------|-------------------|----------|---------|
| | | | | | Target | Current | | | | | | Target | Current |
| M99-048 | II | Dose Ranging, ABECB | 9/1/99 | 3/31/00 | 300 | 384 | | | | | | | |
| M99-053 | II | Dose Ranging, Sinusitis | 9/1/99 | 4/30/00 | 300 | 292 | | | | | | | |
| M99-054 | II | Dose Ranging CAP | 9/1/99 | 4/30/00 | 300 | 187 | | | | | | | |
| M00-219 | III | CAP, Dose Ranging | 11/7/00 | 4/30/01 | 800 | 189 | | | | | | | |
| M00-216 | III | ABECB vs Azithromycin | 11/7/00 | 4/30/01 | 600 | 335 | | | | | | | |
| M00-217 | III | ABECB vs Levofloxacin | 11/7/00 | 4/30/01 | 500 | 16 | | | | | | | |
| M00-225 | III | Sinusitis Dose Ranging | 11/7/00 | 4/30/01 | 600 | 253 | | | | | | | |
| M00-223 | III | Pharyngitis vs Penicillin 500mg TID | 11/7/00 | 4/30/01 | 520 | 411 | | | | | | | |
| M00-222 | III | Pharyngitis vs Penicillin 500mg TID | 11/7/00 | 4/30/01 | 520 | 6 | | | | | | | |

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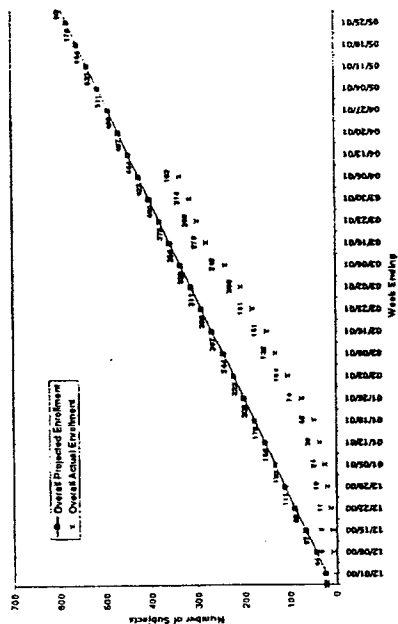
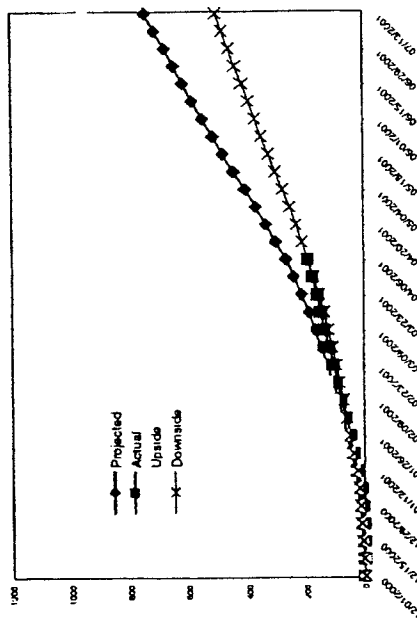
March 2001

ABT-773

Ongoing Clinical Studies (List first time in man, Phase II Dose-Ranging and Pivotal Trials)

Protocol: M00-219 – Dose-Ranging CAP
 Objective: Dose selection.
 ABT-773 Doses: 150mg QD vs 150mg BID, 10 days
 Comparator Doses: None
 Target Enrollment: 800
 Status: Currently enrolling

Major Findings:
 Author: (Double click on name to edit)



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March 2001

ABT-773

Ongoing Clinical Studies (List first time in man, Phase II Dose-Ranging and Pivotal Trials)**Protocol:****Objective:****ABT-773 Doses:****Comparator Doses:****Target Enrollment:****Status:****Major Findings:****M00-217 - Phase III ABECB vs Levofloxacin**

Safety & Efficacy

150 mg QD

Levofloxacin 500mg QD for 7 days

500

Enrollment not yet started.

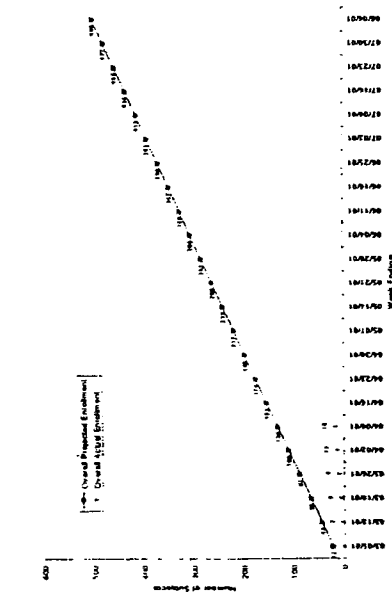
Dose Selection

150mg QD vs 150mg BID, 10 days

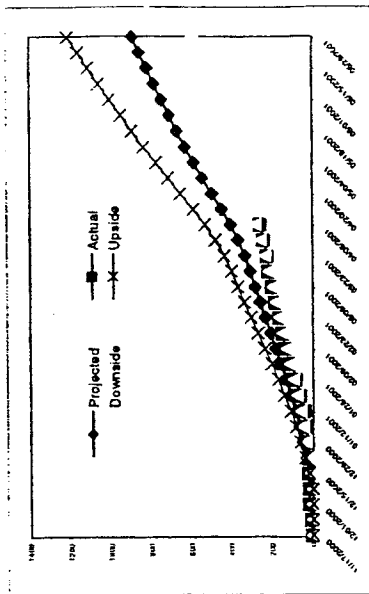
None

600

Currently enrolling

M00-225 - Sinusitis Dose-Ranging

Author:
(Double click on chart to edit)



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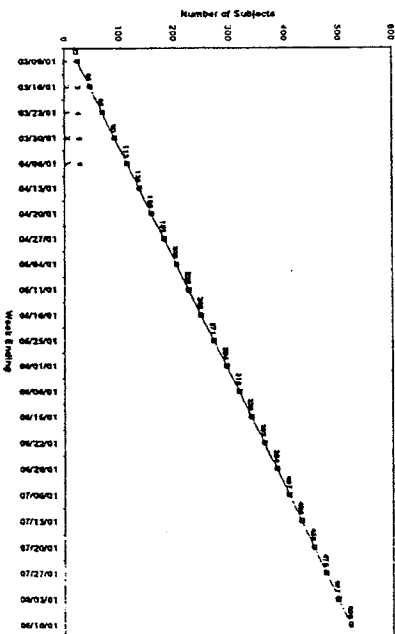
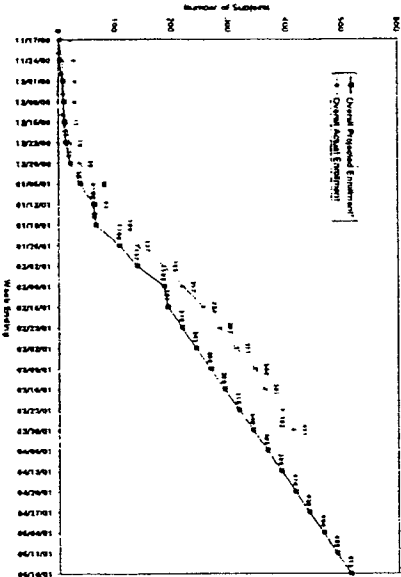
March 2001

ABT-773

Ongoing Clinical Studies (List first time in man, Phase II Dose-Ranging and Pivotal Trials)

Protocol: M00-223 - Phase III Pharyngitis vs Penicillin 500mg TID
Objective: Safety & Efficacy
ABT-773 Doses: 150mg QD, 5days
Comparator Doses: Penicillin 500 mg TID, 10 days
Target Enrollment: 520
Status: Currently enrolling
Major Findings:

M00-222 - Phase III Pharyngitis vs Penicillin 500mg TID
Safety & Efficacy
 150mg QD, 5 days
 Penicillin 500mg TID, 10 days
 520
 Sites initiated, enrollment not yet started



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Abbott Portfolio Review

March 7-9, 2001

- Project/Compound: **ABT-773 Adult Oral Tablet**
- Presenter: **Dr. Carl Craft**
- Project Team Members : **Carol Meyer, Rod Mittag**

ABT-773 Target Product Profile

- **Target Indication:**
 - Respiratory tract infections
- **Targeted unmet medical need:**
 - Activity against resistant organisms
 - Low propensity for resistance development
 - Convenient dosing
 - Very good tolerability
 - Insignificant drug-drug interactions
- **Targeted profile vs gold standard**

| | ABT-773 | Biaxin XL | Zithromax |
|------------------|------------------------------------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------|---------------------------------------------------------------------------------------------------------------------|
| Dosing | ABECB: 150 mg QD x 5 d Phar: 150 mg QD x 5 d CAP: 150 mg QD or BID x 10 d ABS: 150 mg QD or BID x 10 d | All regimens 2 x 500 mg QD ABECB: 7 d CAP: 7 d ABS: 14 d | 250 mg QD x 5 days for ABECB, pharyngitis, and CAP No sinusitis indication; warnings against use in "severe" CAP |
| Efficacy | ABECB: 85% Cure, 88% Erad ABS: 82% Cure, 83% Erad CAP: 84% Cure, 91% Erad Pharyngitis: No clinical data | ABECB: 83-86% Cure, 86-92% Erad ABS: 85% Cure, NA Erad CAP: 89% Cure, 89% Erad | Statistically equivalent curoferendication to comparators; availability of IV adds to efficacy image |
| Adverse Events | Taste perversion: 4% Diarrhoe: 10% Nausea: 5% Vomiting: 2% | Taste perversion: 6% Diarrhoe: 6% Nausea: 3% Vomiting: 1% | Very well tolerated; GI disturbance ~ 2-5%; no taste perversion |
| Resistance Claim | Being pursued | Under exploration | None |

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ABBT 0013203

ABT-773 Key Pre-Clinical Findings

- **Toxicology:**
- Rat:** Target organs : liver, lung, testes, epididymides
NTEL in rat \approx 3.5 -8 x clin AUC
- Monkey:** Target organ: liver
NTEL in monkey \approx 1.5 -4 x clin AUC; Next higher dose of 50mg/kg only showed mild ALT elevation (7 -18 x clin AUC)
- Male fertility** NTEL \approx 2-5 x clin AUC, although next higher dose had effects on sperm concentration and motility, these were reversible within 2 mo.

ABT-773 Key Pre-Clinical Findings

- **Pharmacology:**
- ABT-773 dose-dependently prolonged canine Purkinje fiber repolarization in the absence of plasma protein binding at 5 mcg/mL (10x therapeutic)
 - In the presence of plasma proteins, a concentration of 5 mcg/ml was cleared but 50 mcg/mL was not. (100x therapeutic).
 - In anesthetized dogs, Abbott-195773 produced no significant effect on the corrected QT interval at concentrations up to 8.86 ± 0.27 mcg/ml.
 - As plasma levels increased from 8.86 ± 0.27 to 22.00 ± 0.61 mcg/ml, QTc increased by 40 ± 2 msec or $11 \pm 1\%$.
 - Studies in telemetry-instrumented dogs will be completed by May 1, 2001.

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ABT-773 Key Pre-Clinical Findings

- **Metabolism:** Substrate and inhibitor of Cyp 3A (liver/GI)
Clearance predominantly by hepatic metabolism in dog and rat
Absolute bio about 36-60% (4 species)
One metabolite (N-desmethyl) less active than parent

ABT 773 Microbiology

- Unique mechanism, ribosome binding properties
- Active vs. key respiratory pathogens including macrolide-resistant streptococci
 - Among most active agents for Gram+ pathogens; more active than Aventis' telithromycin
 - Comparable activity to azithromycin/telithromycin for H. influenzae; weakness vs quinolones
- Bactericidal
- Extended post-antibiotic effect (PAE)
- Low rate of resistance development in vitro and in vivo
- AUC/MIC best predictor of outcome

| MIC90 | clarithromycin | trovafloxacin* | telithromycin | ABT-773 |
|----------------------|----------------|----------------|---------------|---------|
| S. Pneumoniae (susc) | < 0.03 | 0.125 | 0.008 | < 0.002 |
| S. Pneumoniae (mef) | 8.0 | 0.125 | 1 | 0.12 |
| S. Pneumoniae (erm) | > 32 | 0.125 | 0.12 | 0.01 |
| S. Pyogenes (mef) | 16 | 0.125 | 1 | 0.12 |
| S. Pyogenes (erm) | > 32 | 0.25 | > 8 | 0.5 |
| M. catarrhalis | 0.03 | 0.015 | 0.25 | 0.25 |
| H. influenzae | 8 | 0.015 | 2 | 2 |

* Withdrawn from market, but among the more potent quinolones

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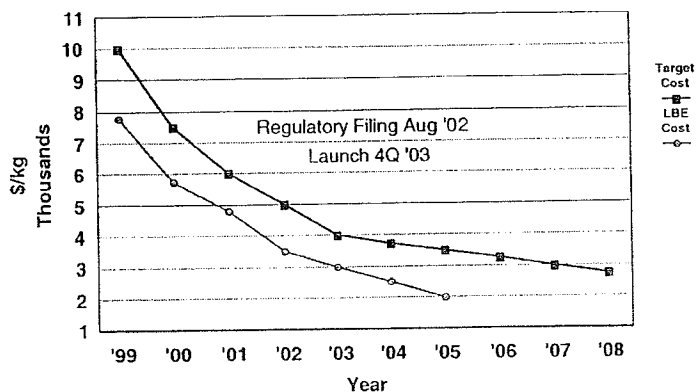
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ABBT 0013205

ABT 773 Chemistry and Manufacturing

▪ Bulk Drug Substance

Cost of Goods based on Current Process



ABT 773 Chemistry and Manufacturing

▪ Drug Product

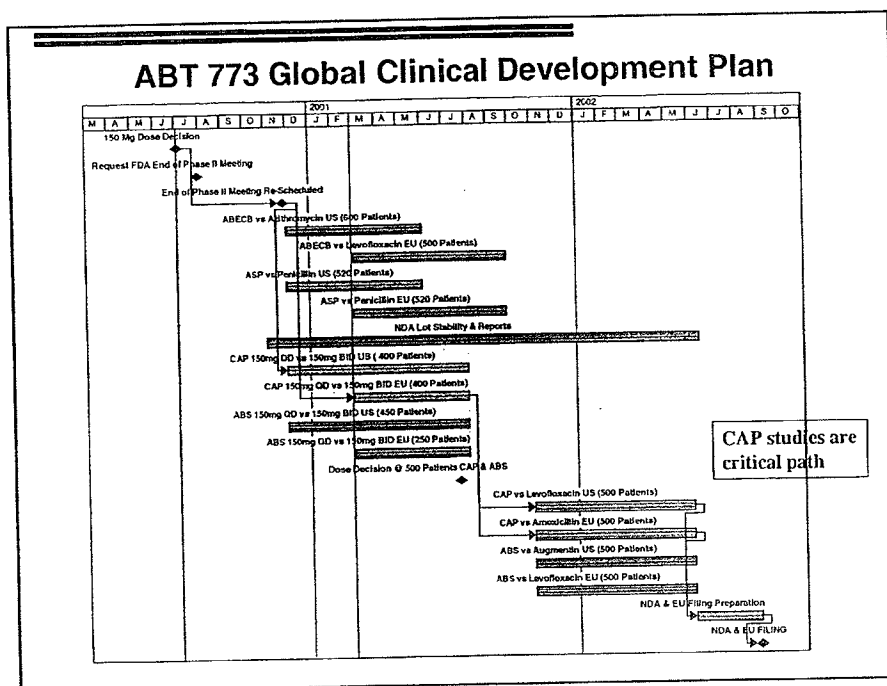
> Description:

- Immediate Release 150mg Coated Tablet
- Commercial Product will be Global
- Planned Source US and UK

> Status:

- Intermediate Scale Product bioequivalent to Registration Lots
- Registration Lots used for Phase 3 studies
- Registration Lot Stability Studies initiated 2/01
- Final US and UK Scale up activities ongoing

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ABT 773 TABLET BUDGET

| | 1997 Phase I | 1998 Phase I | 1999 Phase I/II | 2000 Phase II/III | 2001 Phase III | 2002 to NDA Phase III | Total |
|------------------|-----------------|-----------------|-----------------------|-------------------------|----------------------|-----------------------------|-------|
| Clinical Program | 0.5 | 2.0 | 11.9 | 34.5 | 61.7 | 33.91 | 144.5 |
| CMC | 7.1 | 10.4 | 28.6 | 31.8 | 21.7 | 14.5 | 114.1 |
| Drug Safety | 1.0 | 2.5 | 2.5 | 3.0 | 1.9 | 1.0 | 11.9 |
| Other | 1.7 | 5.7 | 5.3 | 5.3 | 2.7 | 2.5 | 23.2 |
| Total by Year | 10.3 | 20.6 | 48.3 | 74.6 | 88.0 | 51.9 | 293.7 |
| Cumulative | 10.3 | 30.9 | 79.2 | 153.8 | 241.8 | 293.7 | |

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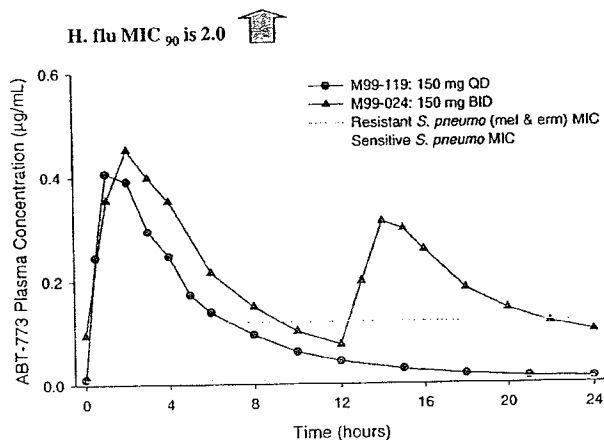
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ABBT 0013207

ABT 773 Phase I Findings

Pharmacokinetics

150 mg QD and 150 mg BID Profiles with *S. pneumo* MICs



ABT 773 Phase II Findings

Combined ABECB, CAP, ABS Clinical Response

| | 150 mg QD | 300 mg QD | 600 mg QD |
|---------------------|---------------|---------------|---------------|
| Clin and Bact. Eval | 84% (42/50) | 90% (103/115) | 88% (106/120) |
| Clin Eval | 88% (168/193) | 88% (247/279) | 81% (216/265) |
| ITT | 83% (176/211) | 82% (259/314) | 75% (230/305) |

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ABT 773 Phase II Findings

Combined ABECB, CAP, ABS Bacteriological Response

Clinically and Bacteriologically Evaluable

| | <u>150 mg QD</u> | <u>300 mg QD</u> | <u>600 mg QD</u> |
|-----------------------|------------------|------------------|------------------|
| <i>S. pneumoniae</i> | 87% (13/15) | 91% (30/33) | 91%(29/32) |
| <i>M. catarrhalis</i> | 84% (16/19) | 84% (21/25) | 84%(16/19) |
| <i>H. influenzae</i> | 87% (20/23) | 94% (33/35) | 77%(37/48) |
| Overall | 86% (49/57) | 90% (84/93) | 83%(82/99) |

ABT 773 Phase II Findings

Combined ABECB, CAP, ABS Adverse Events

All Adverse Events

| | <u>150 mg QD</u> | <u>300 mg QD</u> | <u>600 mg QD</u> |
|------------------|------------------|------------------|------------------|
| GI and Taste | | | |
| Taste Perversion | 4% (8/223) | 17% (55/322) | 27% (87/318) |
| Diarrhea | 10%(22/223) | 11% (34/322) | 19% (60/318) |
| Nausea | 5% (12/223) | 12% (40/322) | 26% (83/318) |
| Vomiting | 2% (4/223) | 6% (19/322) | 14% (44/318) |

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ABBT 0013209

ABT 773 Indications

| Infection | Dosage | Duration |
|---------------------------------------------------------------|------------------|----------|
| Pharyngitis/Tonsillitis due to: <i>S. pyogenes</i> * | 150 mg QD | 5 d |
| Acute bacterial sinusitis due to: | | |
| <i>H. influenzae</i> | 150 mg QD or BID | 10 d |
| <i>M. catarrhalis</i> | 150 mg QD or BID | 10 d |
| <i>S. pneumoniae</i> ** | 150 mg QD or BID | 10 d |
| Acute bacterial exacerbation of chronic bronchitis due to: | | |
| <i>H. influenzae</i> | 150 mg | 5 d |
| <i>H. parainfluenzae</i> | 150 mg | 5 d |
| <i>M. catarrhalis</i> | 150 mg | 5 d |
| <i>S. pneumoniae</i> ** | 150 mg | 5 d |
| Community-acquired pneumonia due to: | | |
| <i>C. pneumoniae</i> | 150 mg QD or BID | 10 d |
| <i>H. influenzae</i> | 150 mg QD or BID | 10 d |
| <i>L. pneumophila</i> | 150 mg QD or BID | 10 d |
| <i>M. pneumoniae</i> | 150 mg QD or BID | 10 d |
| <i>S. pneumoniae</i> ** | 150 mg QD or BID | 10 d |

* Including macrolide-resistant strains.

** Including penicillin-resistant and macrolide-resistant strains.

ABT-773 Phase III Clinical Plan

- **ABECB/ASP comparative studies 150mg QD**
 - Plan to complete in 2000/2001 season
 - Not on critical path to Aug 2002 filing
- **CAP/ABS Dose Ranging 150mg QD vs 150mg BID**
 - Dose selection July 2001 (500 patients per indication)
 - Meet U.S. open-label study requirement for approx. 80-100 bacteriologically evaluable subjects per indication (continue to 800/600 respectively if needed)
- **CAP/ABS comparative studies with selected dose**
 - Initiate Nov 2001 (2 studies each indication, 500 patients/study)
 - 2001/2002 season Northern Hemisphere

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ABT 773 Phase III Clinical Plan

Studies starting in Fall 2001

| Study | Indication | Comparator | Number ABT-773 Subjects | Location |
|---------|------------|--------------|-------------------------------|---------------------|
| M00-221 | CAP | Levofloxacin | 225 | US, Canada (IND) |
| M00-220 | CAP | Amoxicillin | 250 | EU (Non-IND) |
| M00-226 | Sinusitis | Augmentin | 225 | US, Canada (IND) |
| M00-218 | Sinusitis | Quinolone | 250 | EU (Non-IND) |

ABT 773 Regulatory Status

| Region | Proposed Submission Date | Comments |
|--------|-----------------------------|-----------------------------------------------------------------------------------------------------|
| US | August 2002 | |
| Europe | August 2002 | Centralised filing vs Mutual recognition strategy TBD based on strength of the Phase III data |
| Canada | August 2002 | |
| Japan | TBD | Bridging strategy dependent on Ph I results in Japan and Kiko agreement |

**HIGHLY
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Strategic Summary

ABT 773 Key Project Strengths / Positives

- Excellent activity against key resistant respiratory pathogens
- Unique mechanistic advantages (ribosome binding properties)
- Low potential for resistance development
- Market expansion ex-US
- Represents a hedge against Biaxin IR patent expiration in 2004-2005
- Potential for I.V. formulation, expands scope of franchise into new market segment

Strategic Summary

ABT 773 Potential Issues/Threats/Negatives

| Key Issue | Potential Impact |
|----------------------------------------------------------------------------------------------------------------------------------------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Potential for class labeling regarding QT Prolongation effects | Reduced market share due to perceived safety issues |
| Obtaining enough resistant organisms in clinical trials for a resistance claim in product labeling, also FDA desire for severe bacteremic patients | Would need to rely solely on <i>in vitro</i> resistance data for product positioning, potential need for an IV formulation to obtain data on severe patients to support the claim |
| IV Formulation | Need IV formulation to strengthen strategic, commercial, and technical value of product |
| QD vs BID dosing impact on US and ex-US markets | Significant commercial hurdle in the U.S., relatively minor impact ex-US. QD may receive regulatory challenge ex-US; BID dosing has large negative impact on US sales |
| Delayed Phase III program due to delayed FDA EOP II meeting and weak flu season slowing CAP enrollment | Delay to dose selection decision beyond July/Aug 2001 could delay filing |

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ABBT 0013212

ABT-773 Action Plans

| Key Issue | Action Plans |
|----------------------------------------------------------------------------------------------------------------------------------------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Potential for class labeling regarding QT Prolongation effects | <ul style="list-style-type: none"> Conduct EKG monitoring in Phase III to gather additional data on QT prolongation Pursue FDA request for Phase I study in cardiac impaired patients Conduct additional dog tox work to evaluate QT |
| Obtaining enough resistant organisms in clinical trials for a resistance claim in product labeling, also FDA desire for severe bacteremic patients | <ul style="list-style-type: none"> Target patient enrollment to obtain necessary organisms IV formulation would access bacteremic patients |
| IV Formulation | <ul style="list-style-type: none"> Conduct Phase I studies for IV formulation Go/No Go Sep 2001 (\$1MM) based on pain on injection and dose finding |

ABT-773 Action Plans

| Key Issue | Action Plans |
|--------------------------------------------------------------------------------------------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| QD vs BID dosing impact on US and ex-US markets | <ul style="list-style-type: none"> Select dose based on outcome of current QD vs BID trials Minimize regulatory risk Optimize global commercial opportunity |
| Delayed Phase III program due to delayed FDA EOP II meeting and weak flu season slowing CAP enrollment | <ul style="list-style-type: none"> CAP Study sites increased in the US and Europe from 209 to 300 sites Closely manage European site initiations to speed enrollment Implemented investigator incentives Other contingency plans |

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ABBT 0013213

Strategic Summary

ABT 773 Contingency Plans

- 66 sites in the Southern Hemisphere to initiate enrollment in May 2001 should US and European sites not reach enrollment targets by June 2001
 - Dose decision delayed to Sept 2001, filing delayed until Dec 2002
 - Manage US and European study spending due to lower enrollment to offset study costs in the Southern hemisphere
- Other Filing contingencies have been evaluated and are less desirable (regulatory, commercial, logistic)
 - **Option 1:** File Aug 2002 with ABECB/ASP/ABS indications, File Aug 2003 with CAP indication
 - **Option 2:** File in Aug 2002 ABECB/ASP 150mg QD, CAP/ABS 150mg BID
 - **Option 3:** File Dec 2002, all indications, Run 3-arm CAP comparative studies 2001/2002 season
 - **Option 4:** File Aug 2002, Run separate Phase III clinical programs in the U.S. and Europe for CAP and ABS, QD in US, BID ex-US

Strategic Summary

ABT 773 Key Decisions

- A dose decision of 150 mg QD vs 150 mg BID in CAP & sinusitis will be made based on Phase III data by July 2001
- CAP study enrollment is critical path to dose decision milestone
- Delay to dose decision will delay Phase III comparative study initiation currently planned for Nov 2001 and Aug 2002 filing
- Proposed budget (\$MM)

| Thru 2000 | 2001 | 2002 to filing | TOTAL |
|-----------|------|----------------|-------|
| 153.8 | 88.0 | 51.9 | 293.2 |

**HIGHLY
CONFIDENTIAL**

ABT-773 Update March 19, 2001

Agenda

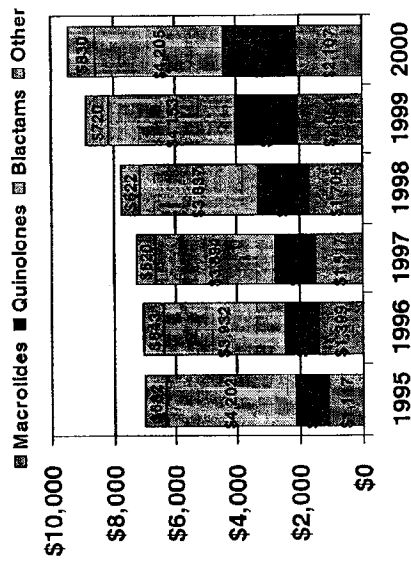
- **Market and trends**
- **Molecule**
- **Microbiology**
- **Pharm/tox**
 - **QT prolongation**
 - **Hepatotoxicity**
- **Clinical development**
 - **Phase I/II summary**
 - **Dose selection**
 - **Phase III program**
 - **Contingency plans**
- **Timeline and budget**
- **IV formulation**
- **Summary of key issues and action plans**

Market and Drivers

- Infectious disease accounts for 13.3 million deaths yearly worldwide, 25% of all deaths
- Antibiotics are the 2nd most commonly prescribed category of drugs
- The global antibiotic market is a \$21B market, the 5th largest global market in sales
- The global antibiotic market has shown modest sales growth
 - 3.9% CAGR₉₆₋₀₀ in sales for overall combined market
 - 4.7% CAGR₉₆₋₀₀ in sales for branded combined market
- Sales growth in the U.S. has been driven by replacement of older generic agents with newer branded agents (most other markets show increasing generic use)
 - Antibiotic resistance results in OBSOLESCENCE of existing agents over time (a CHRONIC problem)
 - Sales per TRX rose from \$18.42 in 1995 to \$28.05 in 2000 (8.8% CAGR)
 - Generics still represent 61% of TRX, representing an opportunity for conversion
- Generics have been more stable ex-U.S

U.S. Market Trends

By Class

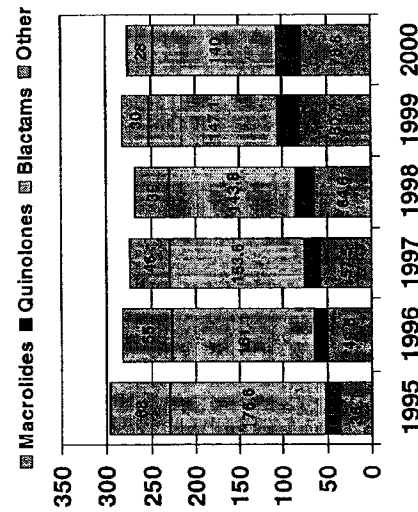


SALES

CAGR₉₅₋₉₉: 6.1%

10.0% Branded

-5.5% Generic



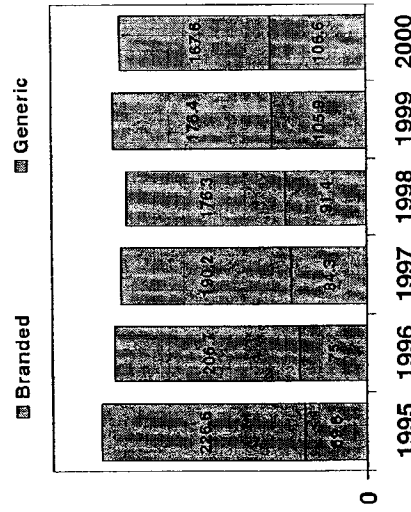
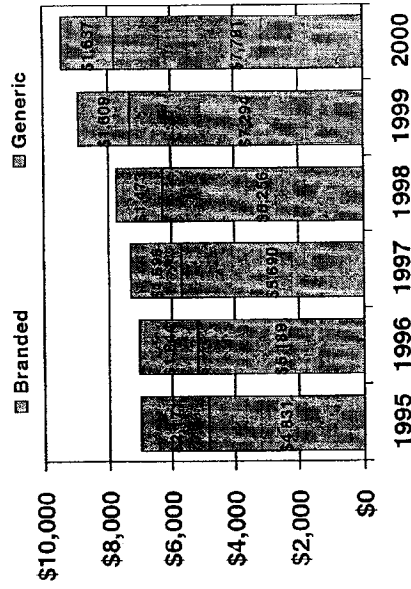
TRX
(excludes IV)

CAGR₉₅₋₉₉: -1.5%

8.9% Branded

-5.9% Generic

Generic vs Brand

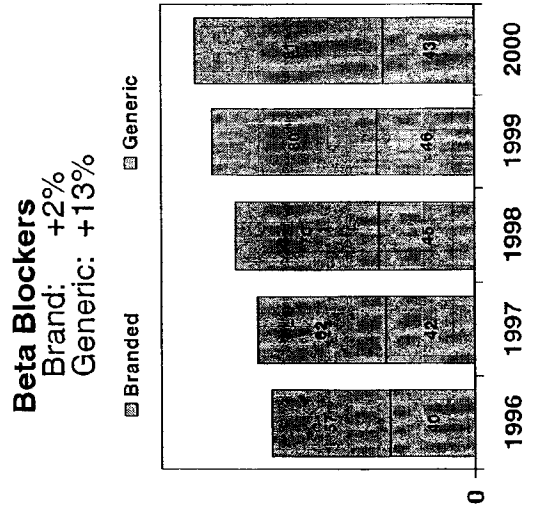
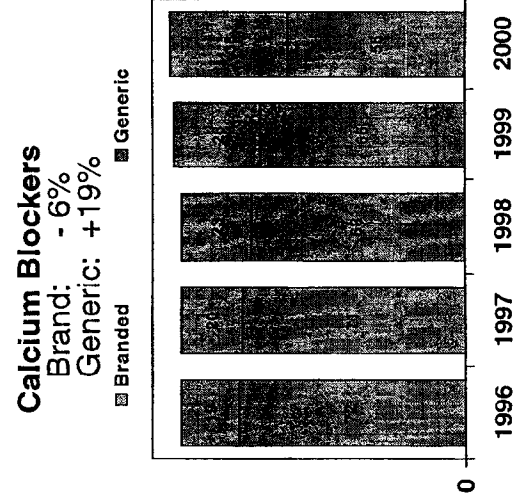
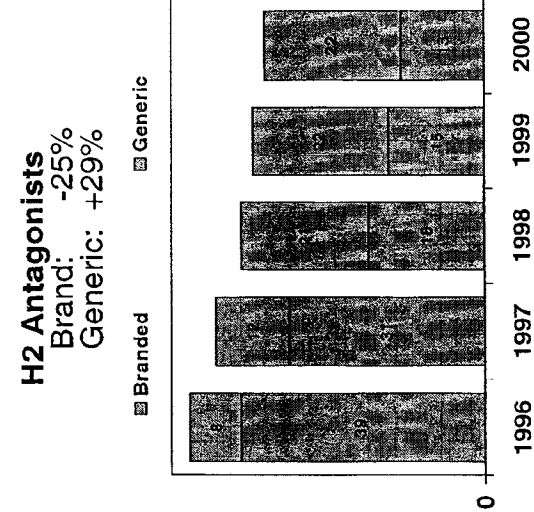
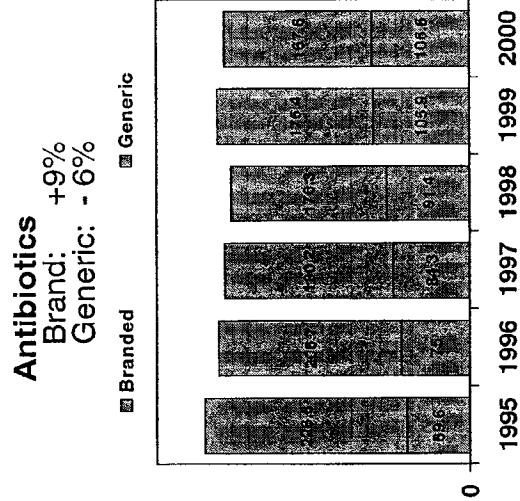


Macrolides and quinolones have driven the growth of the market

Generic use decreasing with increasing antibiotic resistance

While most markets tend toward increasing utilization of generics, the antibiotic market is tending toward decreasing utilization of generics-OBSOLESCENCE

Backup



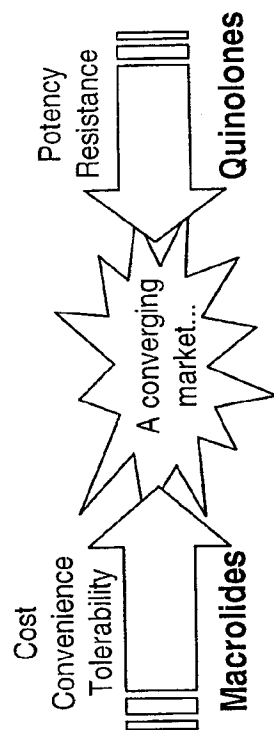
Antibiotic Classes

3 antibiotic classes dominate the market, representing 89% of global sales

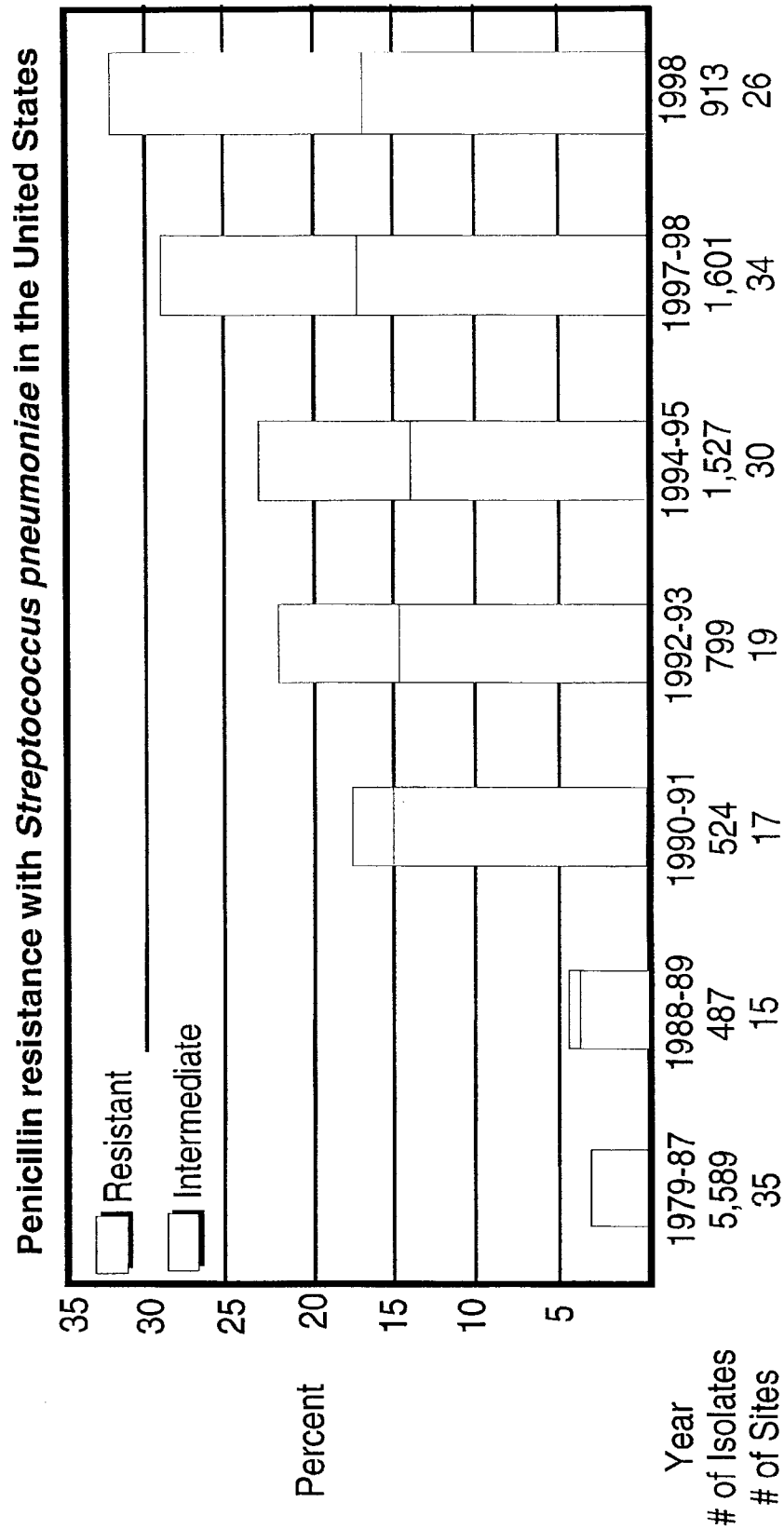
| Class Dominant Brand | Other Brands | Global Class Sales (\$MM) | Ped | IV | Comment |
|----------------------|----------------------------|---------------------------|-----------|----|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| B-lactam Augmentin | Ceftin, Cefzil, pens, amox | \$10,561 | X | X | <ul style="list-style-type: none"> •B-lactams 1.1% CAGR; -1.4% Y-Y •High generic penetration •Augmentin unique, due to resistance |
| Macrolide Zithromax | Biaxin erys | \$4,066 | X | X | <ul style="list-style-type: none"> •Macrolides 8.1% CAGR; 2% Y-Y •Zithromax set new standards in cost, convenience, tolerability •Z growth has slowed (5% Y-Y) due to maturing brand and resistance |
| Quinolone Levaquin | Cipro Tequin Avelox | \$3,750 | Under Dev | X | <ul style="list-style-type: none"> •Quinolones 11% CAGR, 10% Y-Y •Leveraging macrolide resistance to become fastest growing class •New quinolones have overcome narrow spectrum and poor tolerability |

CAGR = Global 1995-2000 compound annual growth rate

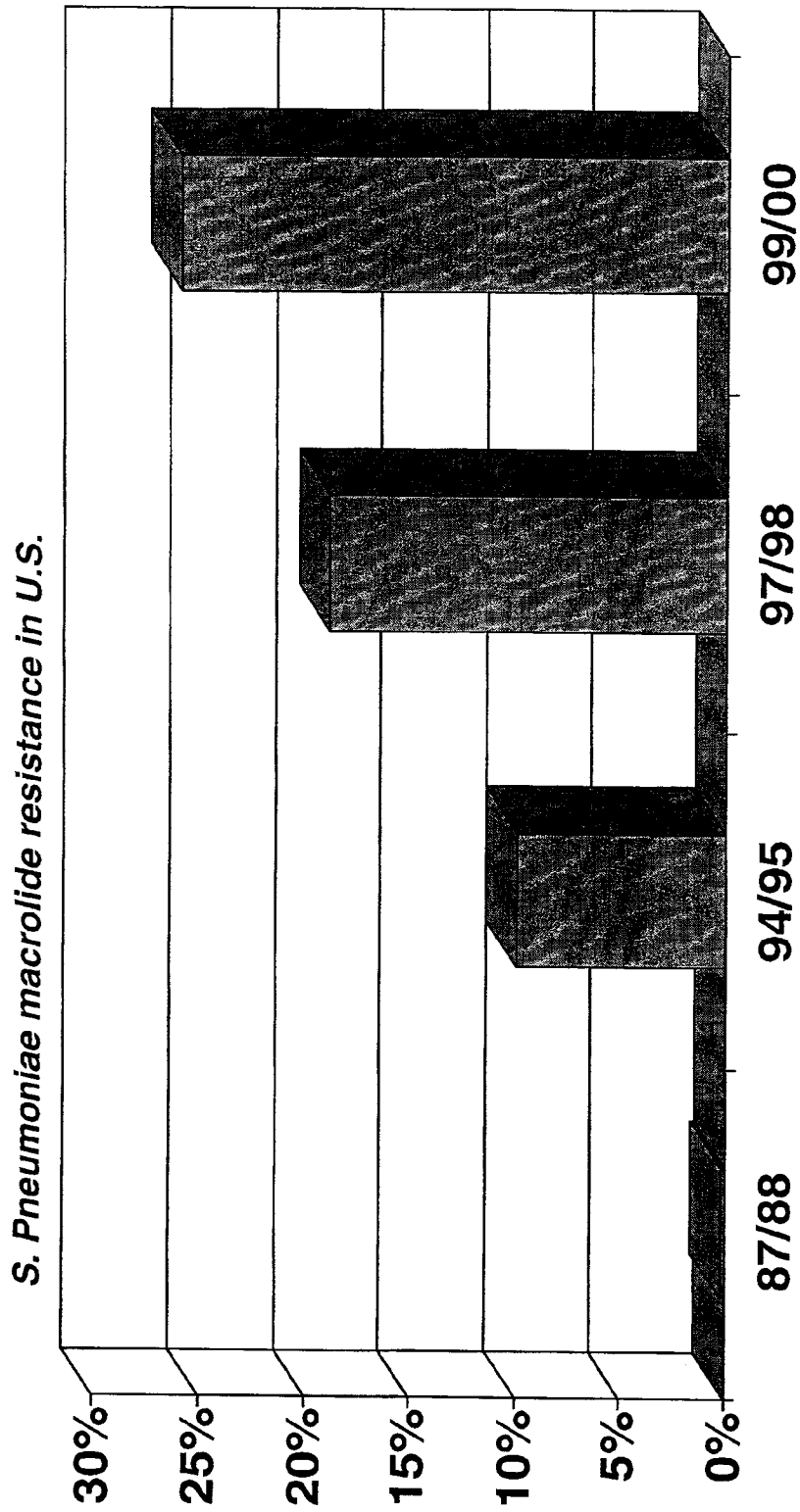
- Macrolides expanded the market on the basis of Pen/B-lactamase resistance, cost, convenience, and tolerability
- Quinolones (+11% CAGR) are now driving the market from a macrolide resistance standpoint (while near parity on cost, convenience, tolerability)



Biaxin and Zithromax were able to leverage increasing Pen resistance to create a compelling selling proposition



Quinolones are now leveraging macrolide resistance in the same fashion to become the fastest growing class

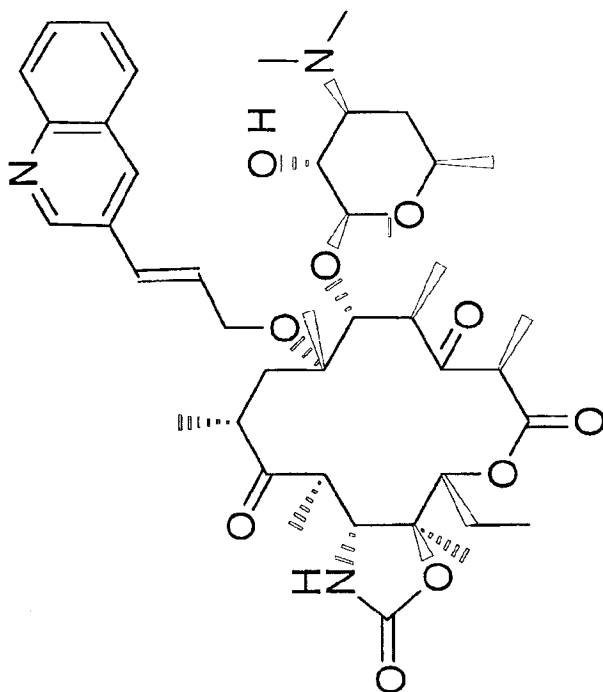


ABT-773 Target Profile

| | ABT-773 | Levaquin | Zithromax |
|------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------|
| Convenience | Target is QD dosing all indications Potential for BID in CAP & sinusitis Duration: 5d, 10 d (parity to Zithromax) PARITY IF QD | All RTI regimens 500 mg QD, 7-14 d | 250 mg QD x 5 days for ABECB, pharyngitis, and CAP No sinusitis indication; warnings against use in "severe" CAP |
| Efficacy | Statistically equivalent cure/eradication to comparators; can take advantage of macrolide/penicillin resistance PARITY | Statistically equivalent cure/eradication to comparators; gold standard for CAP with IV; can take advantage of macrolide/penicillin resistance | Statistically equivalent cure/eradication to comparators; availability of IV adds to efficacy image; subject to increasing levels of macrolide resistance |
| Activity | Most active agent for Gram + pathogens, including telithromycin; parity for atypicals; parity to Zithromax for Gram -, through inferior to quinolones (weakness) | Highly active against most clinically relevant respiratory pathogens; potential issue with increase in Gram - resistance; theories that Gram + quinolone resistance may increase dramatically/rapidly with increased use | Not as active as clari in Gram + pathogens, increasing macrolide resistance, moderate Gram - activity |
| Adverse Events | Taste perversion: 4% Diarrhea: 10% COMPARABLE TO BIAXIN XL | Very well tolerated and safe | Very well tolerated; GI disturbance ~ 2-5%; no taste perversion |
| Resistance Claim | Being pursued; important to development of resistance story; availability of IV will increase likelihood of claim | Claim for pen-R Strep. pneumo | None |
| Price | Parity to Zithromax | \$60 for 7 days | \$43 for 5 days |
| Other | Attempt to leverage "best of both worlds" message i.e. potency & resistance coverage of a quinolone with safety & appropriateness of macrolide | Some class-related negative perceptions among some physicians with respect to AEs and appropriate use, but with increased use these barriers are eroding | |

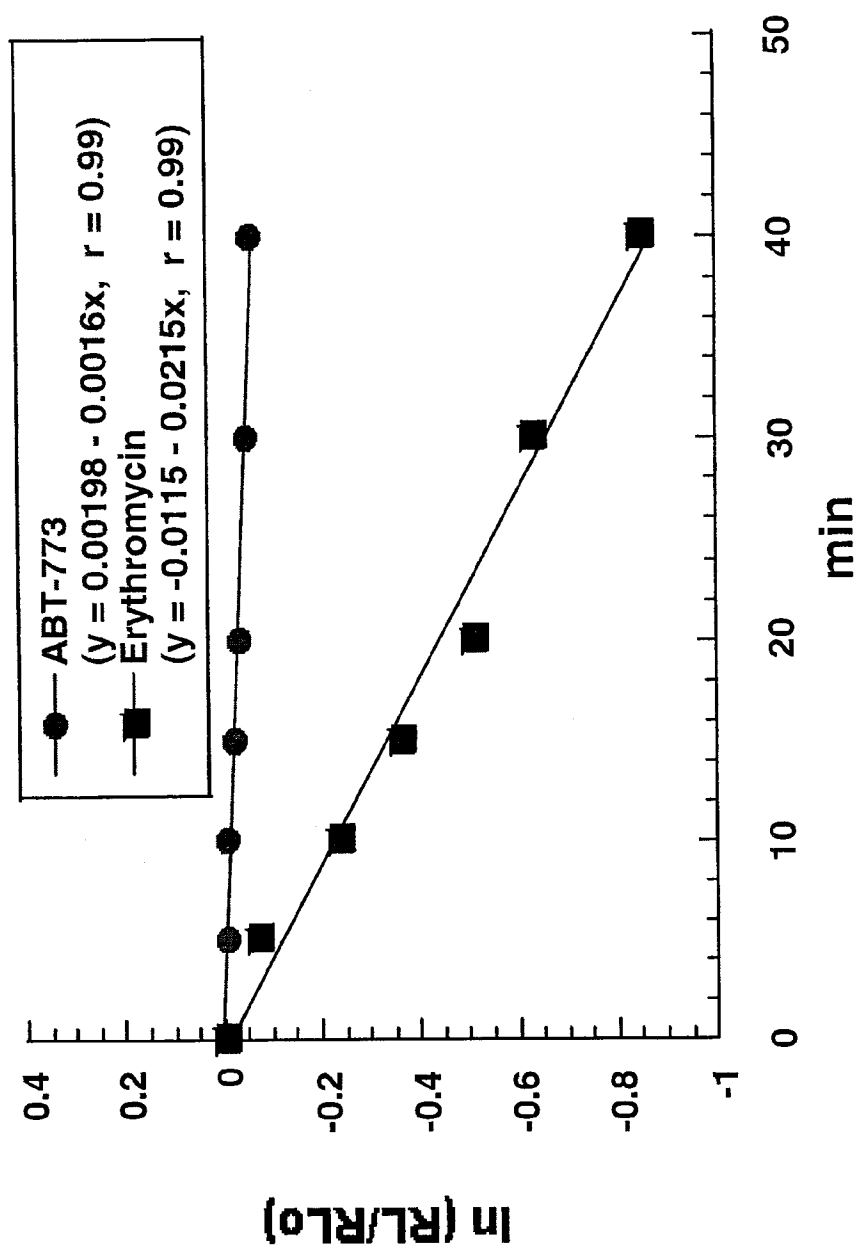
ABT-773 SAR

- Quinolylallyl propenyl moiety at the 6-O –position (↑ PK, activity)
- Carbamate group at the 11, 12-position (↑activity vs macrolide-resistant Strep)
- Keto group at the 3-position (confers *erm* non-induction)



- Bactericidal activity
- Prolonged post antibiotic effect
- Reduced resistance development

ABT-773 Displacement in Susceptible *S. pneumoniae* 2486



J. Capobianco et al.
ICAAC 1999, #2137.

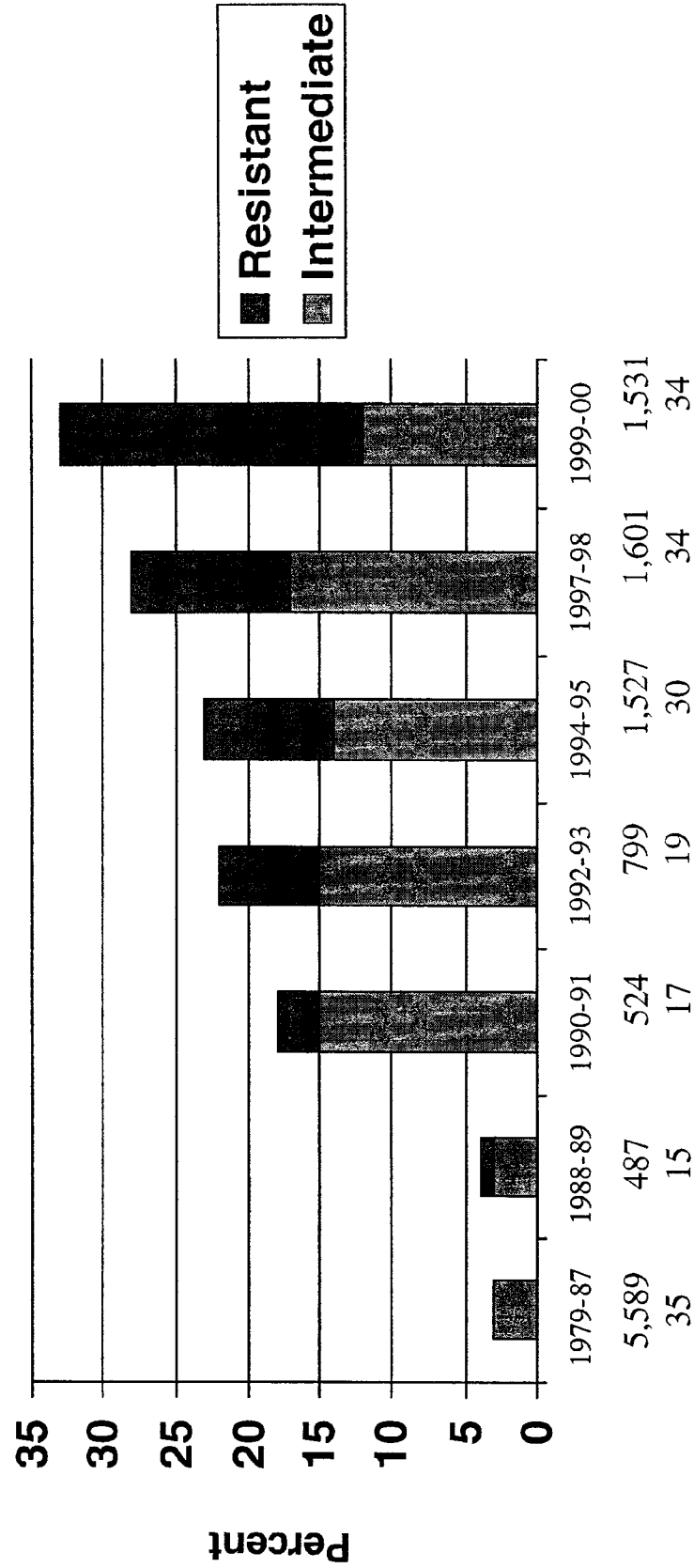
ABT 773 Microbiology

| MIC90 | Clari | Trovan* | Ketek | ABT-773 |
|----------------------|--------|---------|-------|---------|
| S. Pneumoniae (susc) | < 0.03 | 0.125 | 0.008 | < 0.002 |
| S. Pneumoniae (mef) | 8.0 | 0.125 | 1 | 0.12 |
| S. Pneumoniae (erm) | > 32 | 0.125 | 0.12 | 0.01 |
| S. Pyogenes (mef) | 16 | 0.125 | 1 | 0.12 |
| S. Pyogenes (erm) | > 32 | 0.25 | > 8 | 0.5 |
| M. catarrhalis | 0.03 | 0.015 | 0.25 | 0.25 |
| H. influenzae | 8 | 0.015 | 2 | 2 |

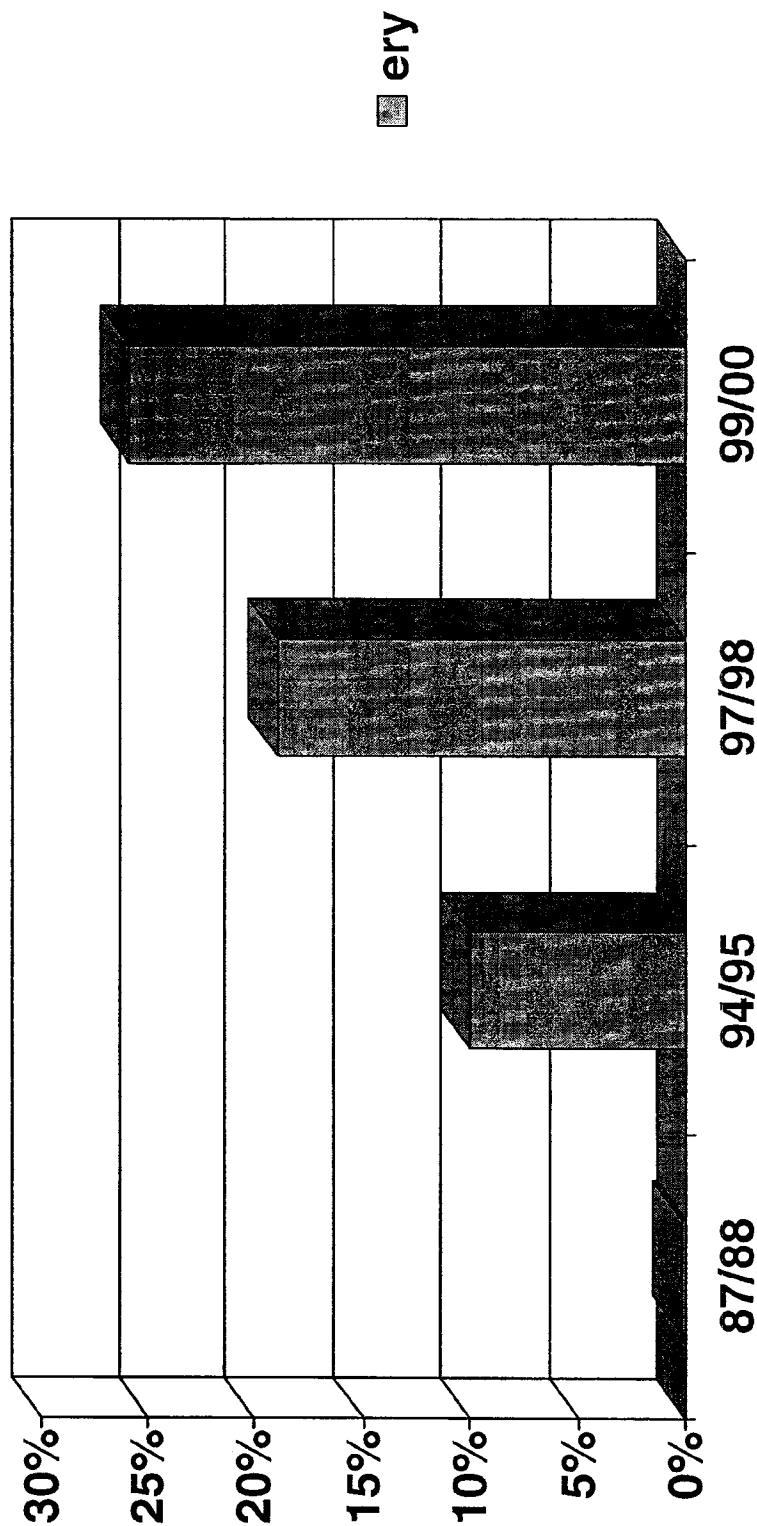
* Withdrawn from market, but among the more potent quinolones

Microbiology

Penicillin resistance with *Streptococcus pneumoniae* in the United States



S. pneumoniae Macrolide Resistance from U.S. Surveillance



US surveillance studies: Doern et al.

Preclinical/Clinical Issues

- QT prolongation
- Hepatotoxicity

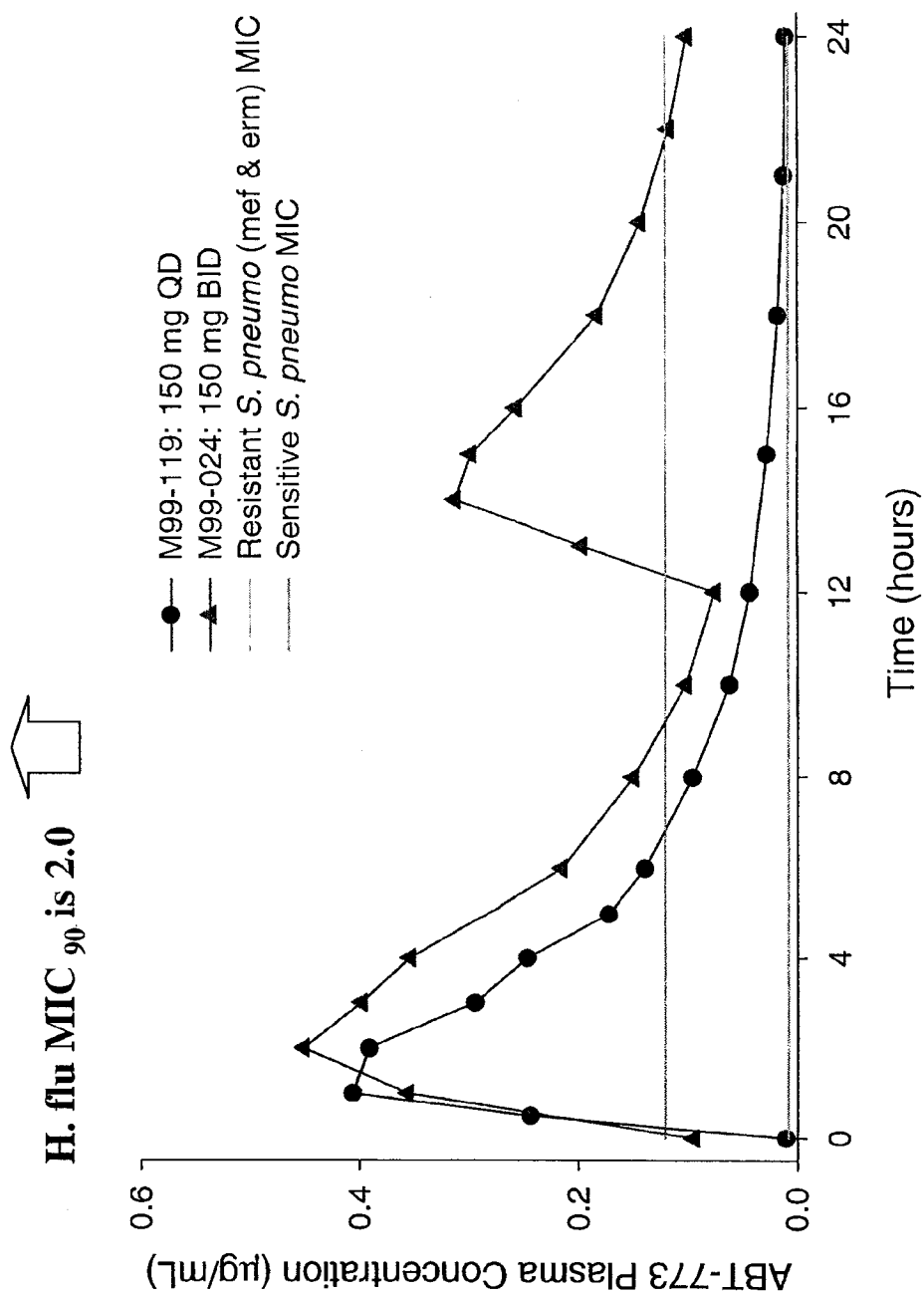
QT Prolongation

- Purkinje fiber repolarization
 - APD increase at 5 mcg/mL (10x clinical Cmax) in the absence of plasma proteins, but not in their presence
 - Moxi > Clari > Ery ~ ABT-773 > Levo (without plasma)
- Dogs
 - no significant effect on QTc up to 9 mcg/mL
 - 11% increase (40 msec) at 22 mcg/mL
 - Telemetry-instrumented dog study requested by FDA will be completed by May 1, 2001
- Humans
 - Possible dose effect in Phase I at daily dose > 800 mg
 - No significant QT effect in ketoconazole interaction study
 - No clinically relevant QT effect in Phase II studies 150 – 600 mg daily (n=412)

Hepatotoxicity

- Toxicology studies
 - NTEL for LFT abnormalities in rat = 3-8 x clinical AUC
 - NTEL for LFT abnormalities in monkey = 2-4 x clinical AUC
- Clinical experience
 - No evidence of LFT issue in Western subjects (<1% asx LFT elevation in >1000 pts in phase II-III studies)
 - Japanese in bridging study showed increased LFTs.
 - 7 of 42 (17%) Japanese subjects had >3x ULN
 - No evidence of dose response
 - Repeat study in Japan showed no evidence of LFT increases in Japanese (n=60) or Caucasians (n=8).

ABT 773 Pharmacokinetics



Phase II Clinical Studies

| Study | Dose/Duration | Number of subjects |
|-----------------|---------------------------------------------|--------------------|
| ABECB | 150, 300 or 600 mg OD Duration: 5 days | N = 384 |
| Acute Sinusitis | 150, 300, or 600 mg OD Duration: 10 days | N = 292 |
| CAP | 300 or 600 mg OD Duration: 7 days | N = 187 |

Phase II Results

Combined ABECB, CAP, ABS Clinical Response

| | <u>150 mg QD</u> | <u>300 mg QD</u> | <u>600 mg QD</u> |
|---------------------|------------------|------------------|------------------|
| Clin and Bact. Eval | 84% (42/50) | 90% (103/115) | 88% (106/120) |
| Clin Eval | 88% (168/193) | 88% (247/279) | 81% (216/265) |
| ITT | 83% (176/211) | 82% (259/314) | 75% (230/305) |

ABT 773 Phase II Findings

Combined ABECB, CAP, ABS Adverse Events

| | <u>150 mg QD</u> | <u>300 mg QD</u> | <u>600 mg QD</u> |
|-------------------------|------------------|------------------|------------------|
| GI and Taste | | | |
| Taste Perversion | 4% (8/223) | 17% (55/322) | 27% (87/318) |
| Diarrhea | 10% (22/223) | 11% (34/322) | 19% (60/318) |
| Nausea | 5% (12/223) | 12% (40/322) | 26% (83/318) |
| Vomiting | 2% (4/223) | 6% (19/322) | 14% (44/318) |

Phase II: 150 mg QD vs 300 mg QD

| Phase IIb Data: Intent-to-treat | | | | | | | | | | |
|---------------------------------|------------------|------------|---------|-------|-------|-----------|-------|-------|---------|-------|
| | | Bronchitis | | CAP | | Sinusitis | | Total | | |
| Clinical Cure | 150 mg QD | 85% | 104/123 | | | 82% | 72/88 | 83% | 176/211 | |
| | 300 mg QD | 83% | 107/129 | 84% | 80/95 | 80% | 72/90 | 82% | 159/314 | |
| | | | | | | | | | | |
| Bacteriological Cure | <i>H. flu</i> | 150 mg QD | 89% | 17/19 | | | 60% | 3/5 | 83% | 20/24 |
| | | 300 mg QD | 81% | 17/21 | 100% | 9/9 | 100% | 7/7 | 89% | 33/37 |
| | <i>S. pneumo</i> | 150 mg QD | 77% | 10/13 | | | 100% | 3/3 | 81% | 13/16 |
| | | 300 mg QD | 90% | 9/10 | 82% | 14/17 | 100% | 8/8 | 89% | 31/35 |

Community-Acquired Pneumonia

Clinical Response

| | 300 mg | 600 mg |
|--|--------|--------|
|--|--------|--------|

| | | |
|---------------------|-------------|-------------|
| Clin and Bact. Eval | 92% (54/59) | 82% (47/57) |
|---------------------|-------------|-------------|

| | | |
|-----------|-------------|-------------|
| Clin Eval | 92% (72/78) | 80% (56/70) |
|-----------|-------------|-------------|

| | | |
|-----|-------------|-------------|
| ITT | 84% (80/95) | 73% (65/89) |
|-----|-------------|-------------|

Phase II summary

- ABT-773 was equally effective at 150 mg QD and 300 mg QD doses in ABECB and ABS
- ABT-773 was efficacious against all target pathogens
- All doses were safe; 150 mg QD was best tolerated for GI events and taste perversion
- 150 mg QD selected for ABECB and pharyngitis in pivotal phase III comparative studies
- 150 mg QD and 150 mg BID will be evaluated to select a regimen for CAP and ABS

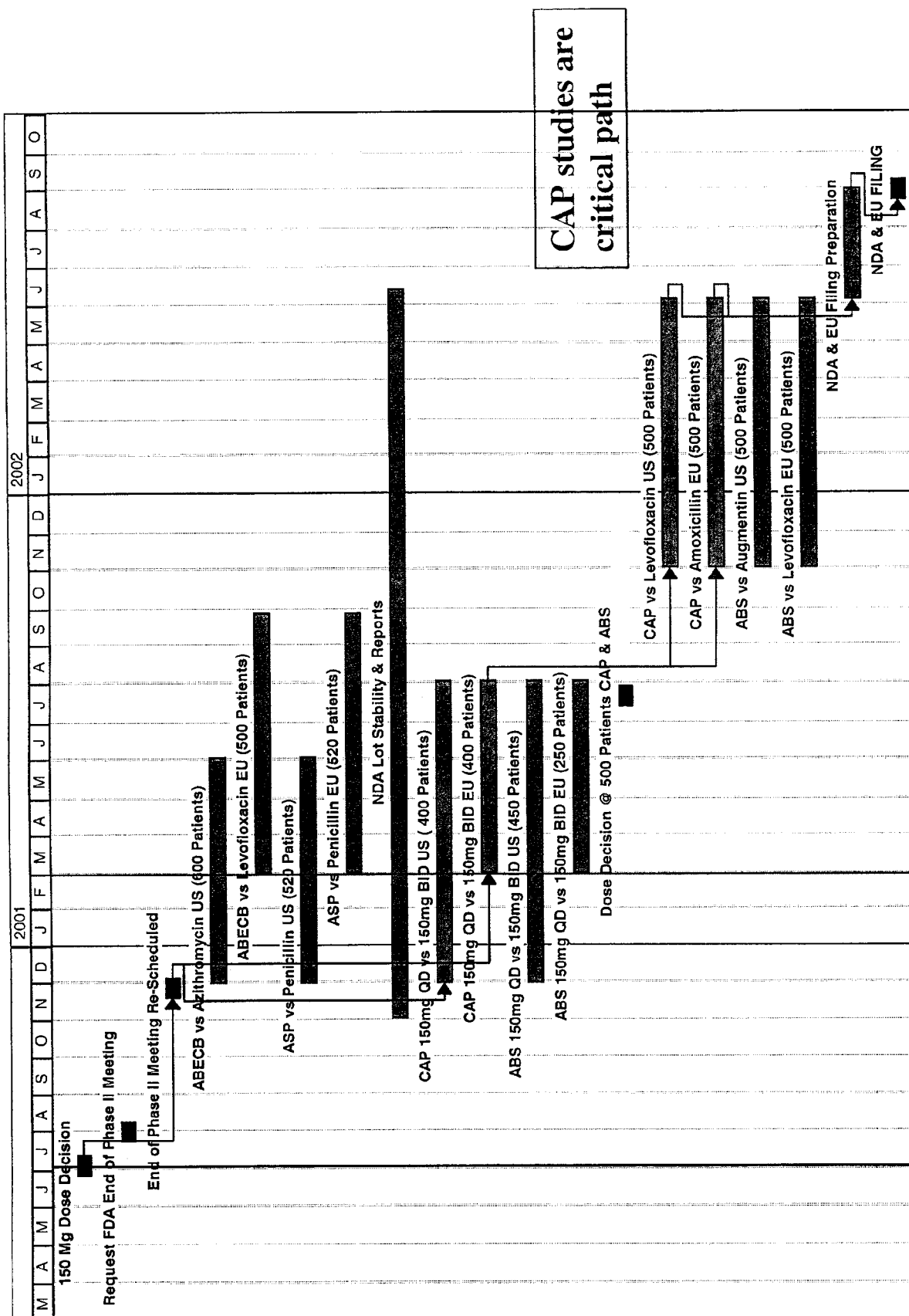
Dose selection: Divergent U.S. and European regulatory and commercial considerations

- **US**
 - Absence of consistent QD dosing for all indications represents a significant commercial hurdle
 - Approval on indication-by-indication basis
- **Europe**
 - Relatively minor commercial impact of BID dosing
 - CAP indication is critical for overall approval

ABT 773 Indications

| Infection | Dosage | Duration |
|------------------------------------------------------------|------------------|-----------------|
| Pharyngitis/Tonsillitis (ASP) | 150 mg QD | 5 d |
| Acute bacterial exacerbation of chronic bronchitis (ABECB) | 150 mg QD | 5 d |
| Acute bacterial sinusitis (ABS) | 150 mg QD or BID | 10 d |
| Community-acquired pneumonia (CAP) | 150 mg QD or BID | 10 d |

ABT 773 Development Timeline



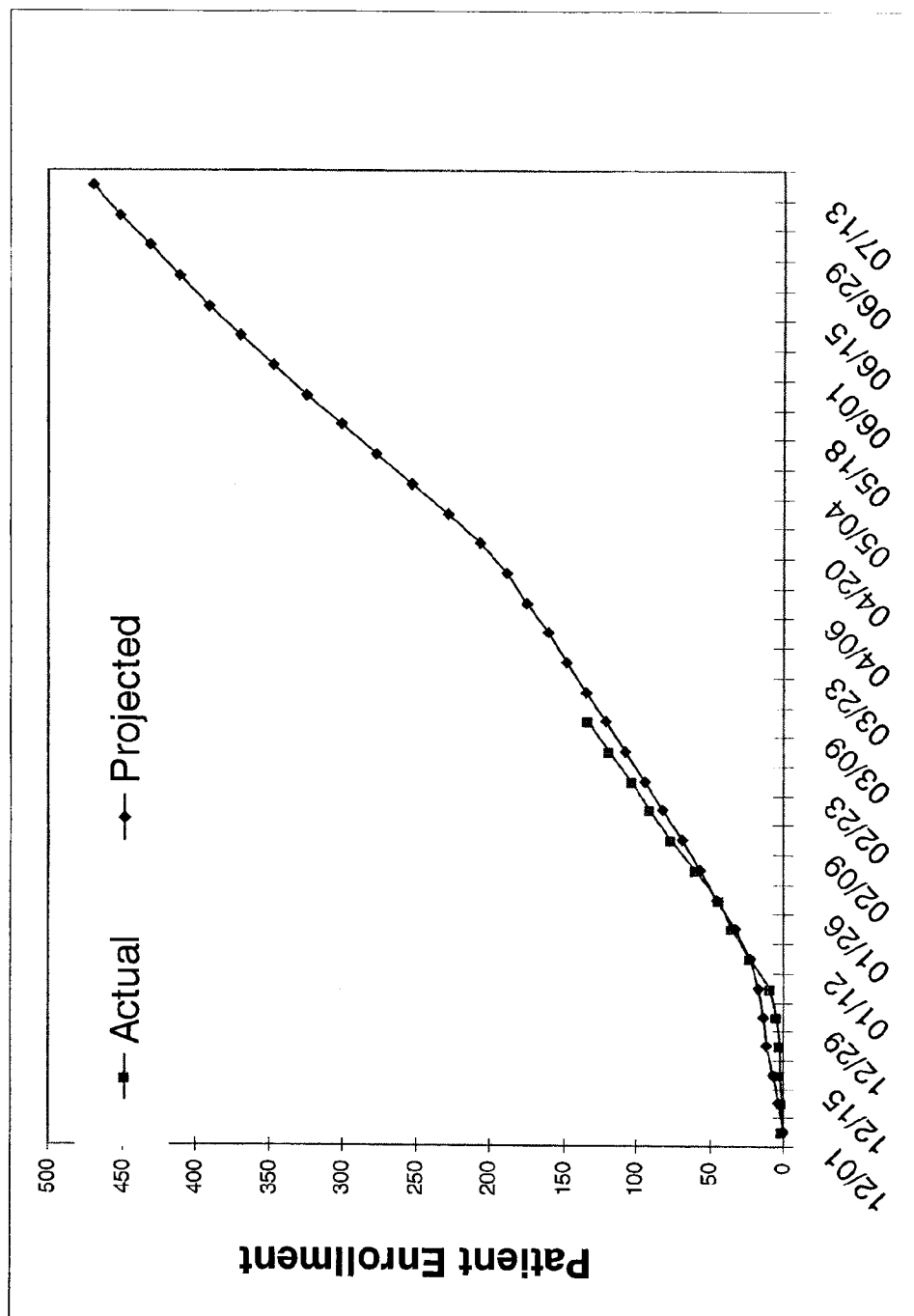
Phase III: ABECB and ASP

| Study | Target Enrollment | Start Date | Location | Enroll Status | # sites |
|-------------------------------------|-------------------|------------|----------|---------------|---------|
| M00-216 ABECB vs Azithromycin | 600 | Nov. 2000 | US | 277 | 110 |
| M00-217 ABECB vs Levofloxacin | 500 | Jan. 2001 | EU | 2 | 100 |
| M00-222 ASP vs Penicillin | 520 | Jan. 2001 | EU | 1 | 45 |
| M00-223 ASP vs Penicillin | 520 | Nov. 2000 | US | 337 | 45 |

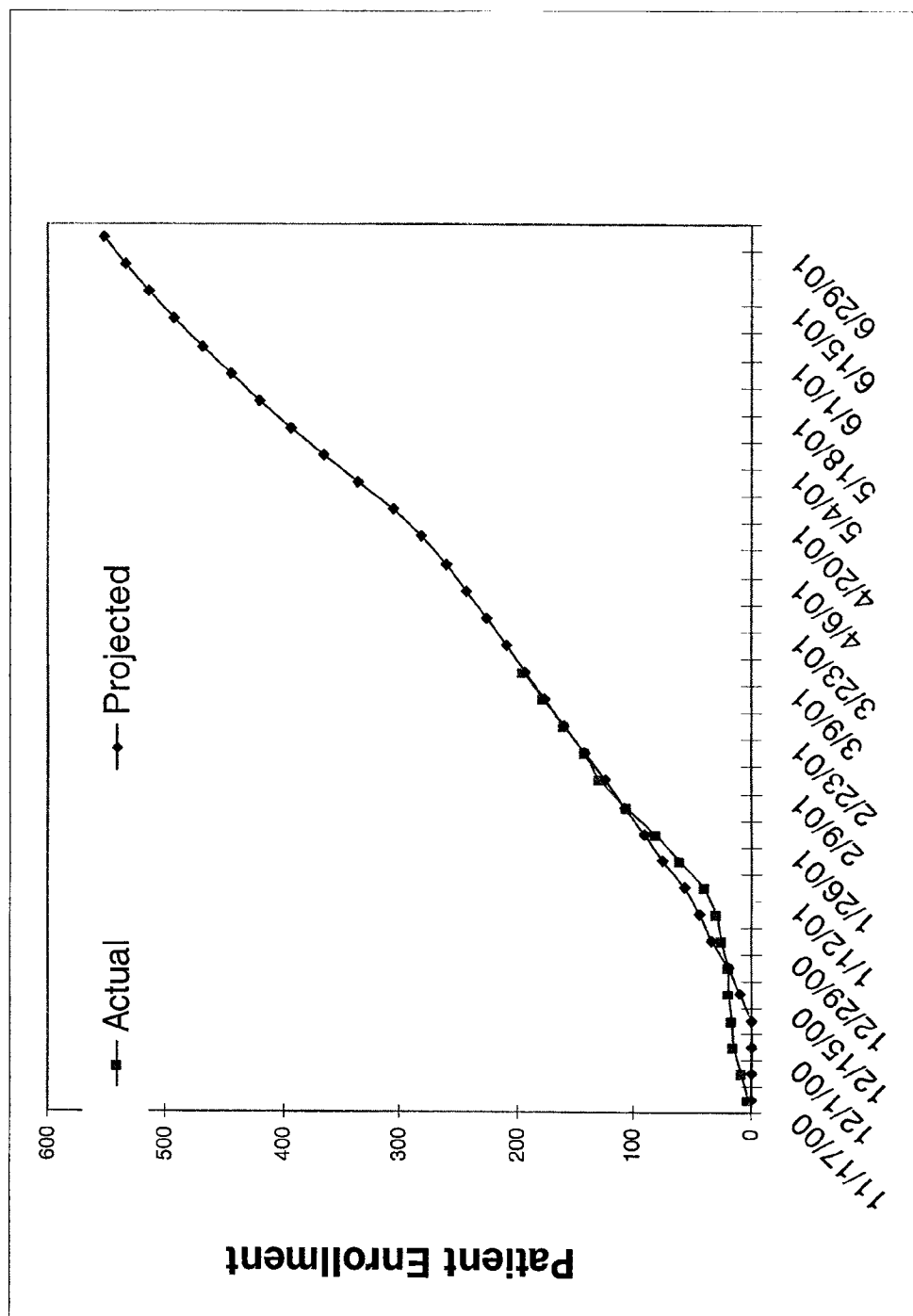
Phase III: CAP and ABS

| Study | Target Enrollment | Start Date | Location | Enroll Status | # sites |
|--------------------------------|------------------------|------------|----------|---------------|---------|
| M00-219 CAP 150mg QD vs BID | 500 for dose selection | Nov. 2000 | US, EU | 143 | 294 |
| M00-221 CAP vs Levofloxacin | 500 | Nov. 2001 | US | | 200 |
| M00-220 CAP vs Amoxicillin | 500 | Nov. 2001 | EU | | 200 |
| M00-225 ABS 150mg QD vs BID | 500 for dose selection | Nov. 2000 | US, EU | 205 | 114 |
| M00-218 ABS vs Augmentin | 500 | Nov. 2001 | US | | 90 |
| M00-226 ABS vs Levofloxacin | 500 | Nov. 2001 | EU | | 90 |

CAP dose-ranging study: enrollment status



Sinusitis dose-ranging study: enrollment status



Progress towards resistance claim

| Pathogen | M00-216 ABECB | M00-219 CAP | M00-225 ABS |
|---------------------------------------------|------------------|----------------|----------------|
| Subjects with Positive culture | 266 | 60 | 77 |
| <i>S. Pneumoniae</i> isolates | 16 | 16 | 19 |
| Resistant <i>S.pneumo</i> | 7 | 9 | 7 |
| <i>Penicillin resist</i> | 0 | 1 | 1 |
| <i>Macrolide resist</i> | 2 | 0 | 3 |
| <i>PRSP & MRSP</i> | 5 | 8 | 3 |
| # of isolates proposed for resistance claim | | | |
| PRSP | 15 | 15 | 15 |
| MRSP | 15 | 15 | 15 |

ABT 773 Contingency Plan

- 66 sites in the Southern Hemisphere to initiate enrollment in May 2001 should US and European sites not reach enrollment targets by June 2001
- Dose decision delayed to Sept 2001, filing delayed
- Manage US and European study spending due to lower enrollment to offset study costs in the Southern hemisphere

2001 Clinical Budget (\$MM)

| | |
|-----------------------------------------------------------------------------------------------------|------|
| • 2001 Clinical Program | 61.7 |
| • Assumptions to achieve budget | |
| • Complete 2000/01 Phase III Studies by June 2001 in U.S. and Europe | |
| • Initiate 2001/02 Phase III Studies by Nov. 2001 | |
| • Conduct start up activities only in Southern Hemisphere, do not initiate enrollment | |
| • Contingency costs | 2.0 |
| • Assumptions | |
| • Continue European ABECB and ASP studies to Dec 2001 | |
| • Enroll CAP and ABS studies in the Southern Hemisphere through Sept. 2001 | |
| • Partial cost offset due to lower enrollment in U.S. and Europe | |

Other Filing Options

Other filing options have been evaluated and are less desirable (regulatory, commercial, logistic)

| Option | Indications | Dose | Filing Date US | Filing Date Europe |
|--------------------------------------------------------------------------------|----------------------------------|---------------------------------|-------------------|-----------------------|
| Option 1 File without CAP indication in the U.S., delay Europe filing | ABECB/ASP/ABS | 150mg QD | Aug 2002 | June 2003 |
| | CAP | 150mg QD or BID | Aug 2003 | June 2003 |
| Option 2 Make BID dose decision for CAP and ABS now. | ABECB/ASP | 150mg QD | Aug 2002 | Aug 2002 |
| | CAP/ABS | 150mg BID | Aug 2002 | Aug 2002 |
| Option 3 Delay Dose Decision to Phase III | ABECB/ASP/ABS 3 arm CAP Study | 150mg QD or BID | Dec 2002 | Dec 2002 |
| Option 4 Run separate US and European clinical programs | ABECB/ASP | 150mg QD | Dec 2002 | Aug 2003 |
| | CAP/ABS | 150mg QD US 150mg BID Europe | Dec 2002 | Aug 2003 |

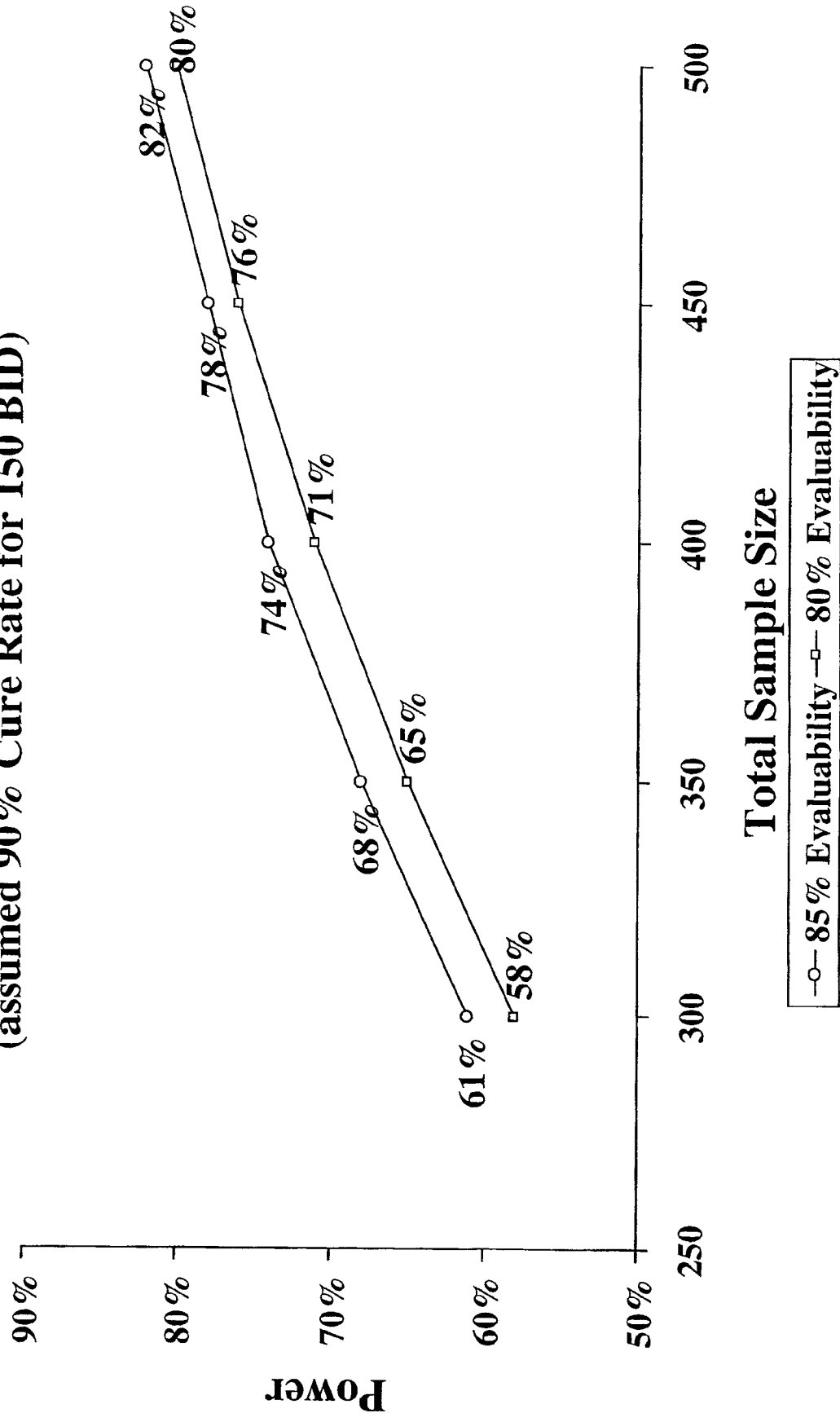
Possibilities

- Make enrollment targets on time
- A little behind
- Way behind

Activities-to-date to address CAP enrollment

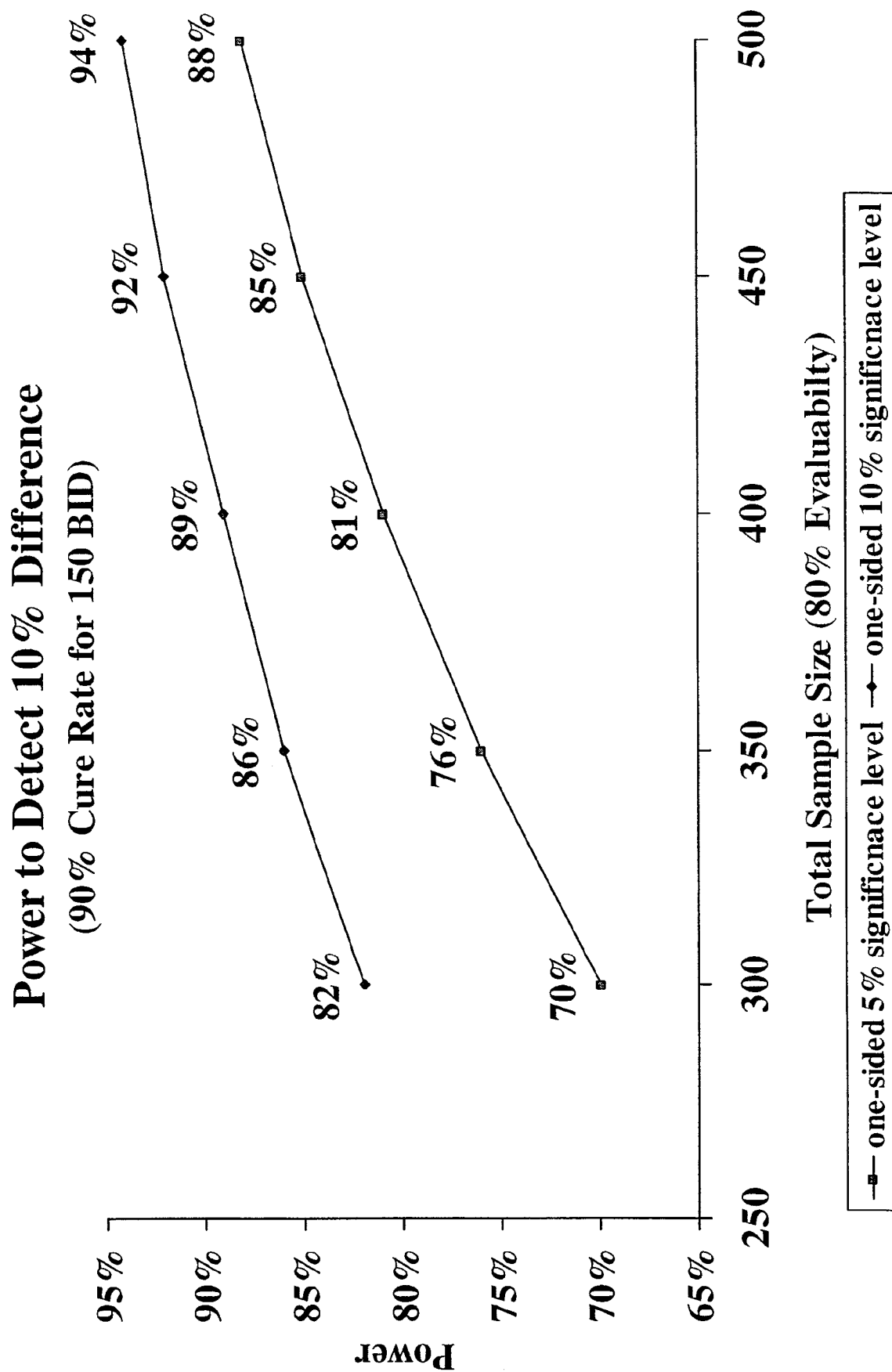
- Increased European sites from 79 to 130 in Nov. 2000
- Site approvals expedited
 - Amendments translated and submitted to Ethics Committees for 350 sites in 1 month
 - CRO actively encouraging investigators to expedite EC approval process as much as possible
- Increased investigator fees
- Increased site follow up/communication
- Diligent CRO management

Power to Detect 10% Difference (assumed 90% Cure Rate for 150 BID)



Statistical power is a function of:

- Sample size
- Treatment arm differences
- Level of statistical significance



Possible outcomes of dose-ranging studies

QD is:

| CAP | Sinusitis | Decision |
|-------|-----------|------------------|
| Worse | Worse | BID |
| Same | Worse | BID |
| Worse | Same | BID or BID/QD |
| Same | Same | QD |

Agenda

- Market and trends
- Molecule
- Microbiology
- Pharm/tox
 - QT prolongation
 - Hepatotoxicity
- Clinical development
 - Phase I/II summary
 - Dose selection
 - Phase III program
 - Contingency plans
- Timeline and budget
- IV formulation
- Summary of key issues and action plans

ABT-773 IV Formulation Strategic, Commercial, and Technical Value

- **Strategic Value**
 - IV represents a channel not currently served by Anti-infective Franchise
 - Leverages presence of MCRs and experience with ID community
- **Commercial Value**
 - IV availability improves formulary access to molecule
 - Potential advantage over telithromycin, which will not have an IV
 - Would be competitive with Zithromax, Tequin, Avelox which have IV
 - Positive impact on tablet formulation
 - estimated \$36MM incremental to peak tablet sales due to step-down therapy
 - Enhances overall “potency” image of brand
- **Technical Value**
 - Support for *S. pneumoniae* Resistance claim
 - FDA indicated that bacteremic patients will be important to establish body of evidence for this claim
 - Provides additional information on QT effects

ABT-773 IV

Planned Clinical Program

- | | |
|------------------------------------------------------------------------------------------------------------------------------------------------------------------------|--------|
| • Single Dose-rising Phase I study | May/01 |
| • Multiple Dose Phase I with selected dose | Aug/01 |
| • File US IND | Nov/01 |
| • Initiate Phase III <ul style="list-style-type: none">– 2 step-down CAP studies (US/Europe)– 2-3 days dosing– Two seasons to complete | Jan/02 |
| • Filing | Dec/03 |

- IV launch currently lags tablet launch by 1 year
 - further delays will reduce the potential value

IV Development Cost

| | Thru 2000 | 2001 | 2002 | 2003 to NDA | Total |
|-----------------------------------------------------|--------------|------|------|-------------------|-------|
| Clinical Program | 0.2 | 4.0 | 6.0 | 2.5 | 12.7 |
| Phase I Single Rising Dose | | 0.5 | | | 0.5 |
| Phase I Multiple Dose | | 0.4 | | | 0.4 |
| Phase III 2 step-down CAP Studies (US/Europe) | | 2.9 | 6.0 | 2.5 | 11.4 |
| CMC | 1.0 | 2.5 | 1.8 | 1.3 | 6.6 |
| Drug Safety/Other | 1.0 | 1.0 | 1.0 | 1.0 | 4.0 |
| Total by Year | 2.2 | 7.5 | 8.8 | 4.8 | 23.3 |

Summary: Key Issues

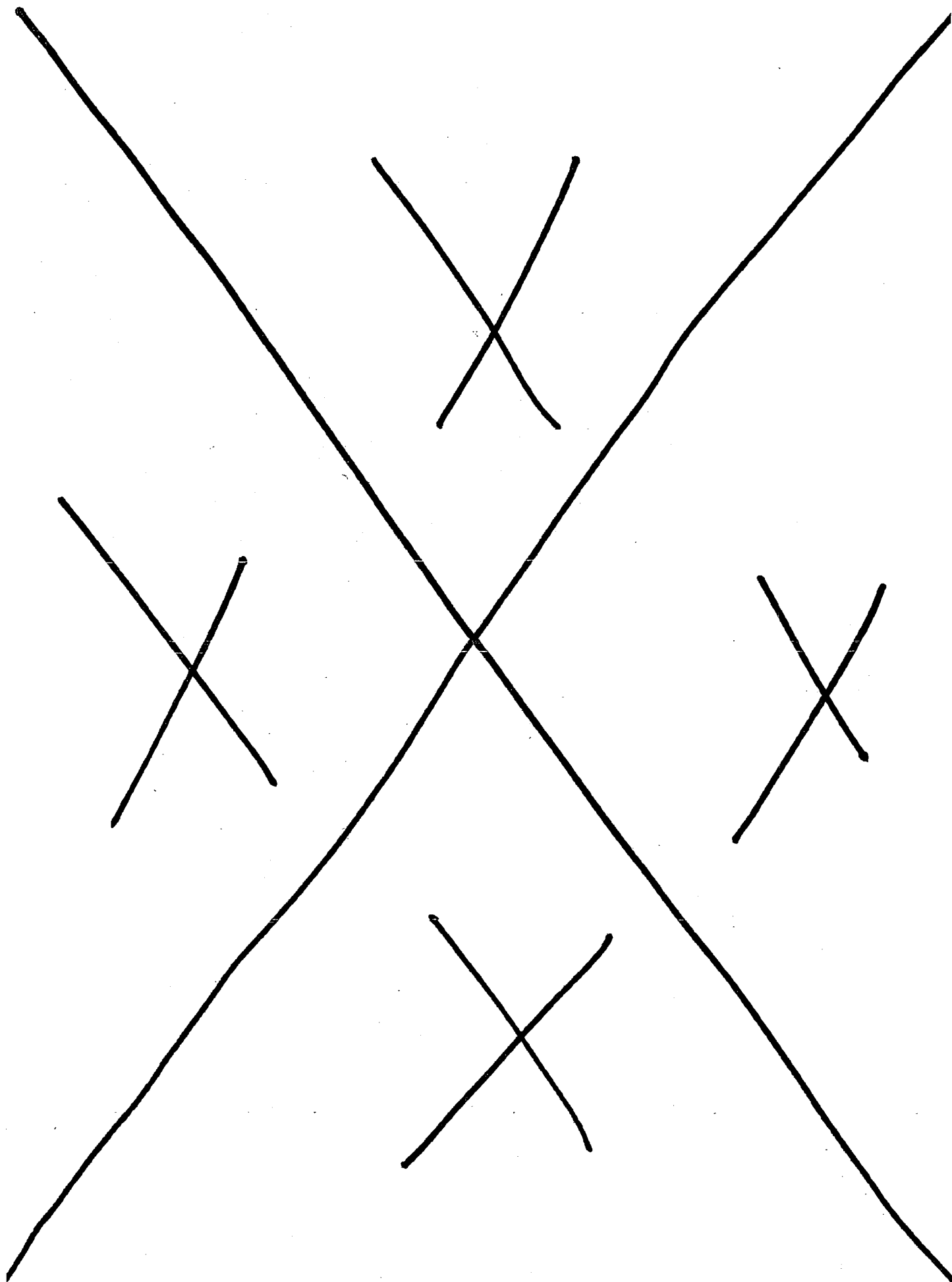
- **QT Prolongation**
 - Possible class labeling, with resulting safety perception
- **Resistance claim**
 - Key differentiating feature
 - Bacteremic isolates requested by FDA requires IV
- **IV Formulation**
 - Strengthens strategic, commercial, and technical value of product
- **QD vs BID dosing**
 - Divergence regulatory and commercial considerations in US vs Europe
- **Delayed Phase III program**
 - Delayed dose selection decision beyond July/Aug 2001 could delay filing

ABT-773 Action Plans

| Key Issue | Action Plans |
|-------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| QT Prolongation | <ul style="list-style-type: none"> ▪ Conduct EKG monitoring in Phase III to gather additional data on QT prolongation ▪ Anticipate and fulfill regulatory expectations for animal and human data |
| Resistance claim | <ul style="list-style-type: none"> ▪ Accrue sufficient patients to obtain necessary organisms ▪ IV formulation would access bacteremic patients |
| IV Formulation | <ul style="list-style-type: none"> ▪ Conduct Phase I studies for IV formulation Go/No Go Sep 2001 (\$1MM) based on pain on injection and dose finding |

ABT-773 Action Plans

| Key Issue | Action Plans |
|---------------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| QD vs BID dosing | <ul style="list-style-type: none">▪ Select dose based on outcome of current QD vs BID trials▪ Minimize regulatory risk▪ Optimize global commercial opportunity |
| Delayed Phase III program | <ul style="list-style-type: none">▪ CAP Study sites increased in the US and Europe from 209 to 300 sites▪ Southern hemisphere contingency▪ Re-evaluate other contingency plans |



ABT-773 DOSING OPTIONS

July 25, 2001

07/23/2001

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ABT-773 Decision Analysis Core Team

Anti-infective Venture

Stan Bukofzer
Vijay Yeldandi
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AI Regulatory Affairs

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Clinical Statistics

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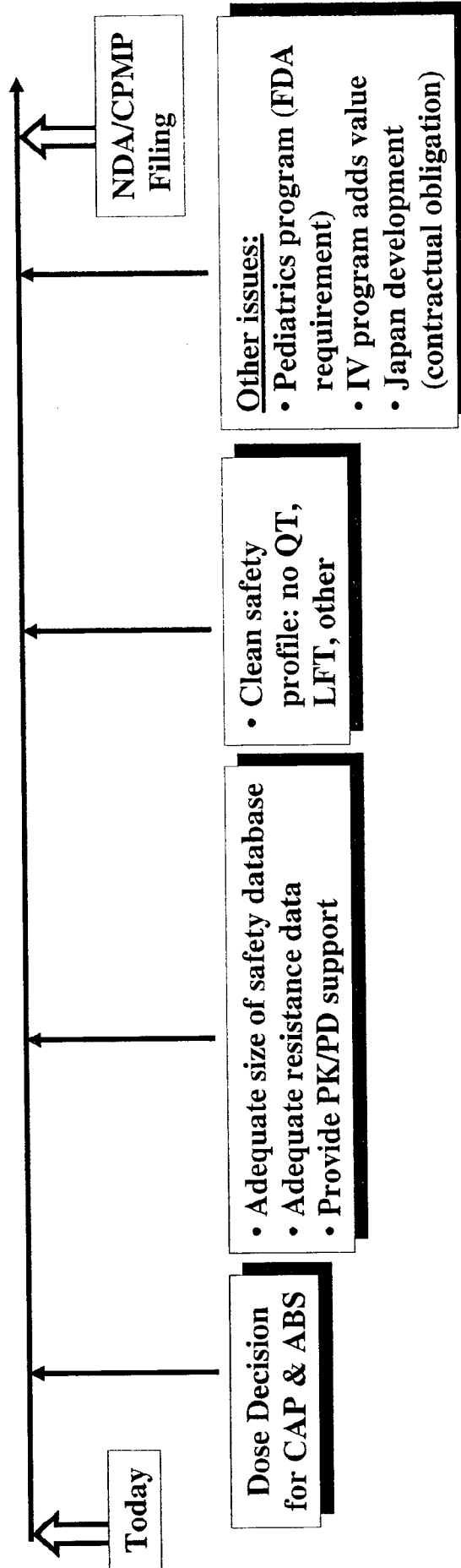
Meeting Agenda

- Summary of ABT-773 strategic analyses.
- Impact of the Ketek advisory on the ABT-773 clinical development program.
- Strategic alternatives for CAP & ABS dose selection.
 - ✧ Status of current dose-ranging studies.
- Risks & trade-offs.
 - ✧ Launch date vs. dose trade-off.
 - ✧ Differential benefit/risk ratios for QD and BID doses.
- Team recommendations.

- Increase in program size to satisfy safety database and resistance claim requirements.

- Given the current blinded ABS trend, the expected value of selecting the BID dose today exceeds the value of waiting for the dose-ranging data.
- The earlier launch date, reduced technical risk, and option to pursue a Ph IV QD line extension outweigh the adverse commercial impact of launching at the BID dose.

Filing date dependant on timing of dose decision and Program size. Program dependant on technical and regulatory hurdles



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Ketek advisory defined new regulatory standards which influences program size:

- Size of the safety database is driven by the product **benefit/risk** profile:
 - Adequacy of Ketek's 3200 patient safety database questioned, ?liver/QT.
- A **resistance claim** will significantly support benefit risk:

| Isolates Needed | % CAP patients with PRSP/MRSP | | |
|-----------------|-------------------------------|------|------|
| | 1.4% | 1.6% | 3.2% |
| 17 | 1236 | 1063 | 531 |
| 25 | 1818 | 1563 | 781 |
| 30 | 2182 | 1875 | 938 |

- **Importance of CAP emphasized with Sinusitis in supportive role**

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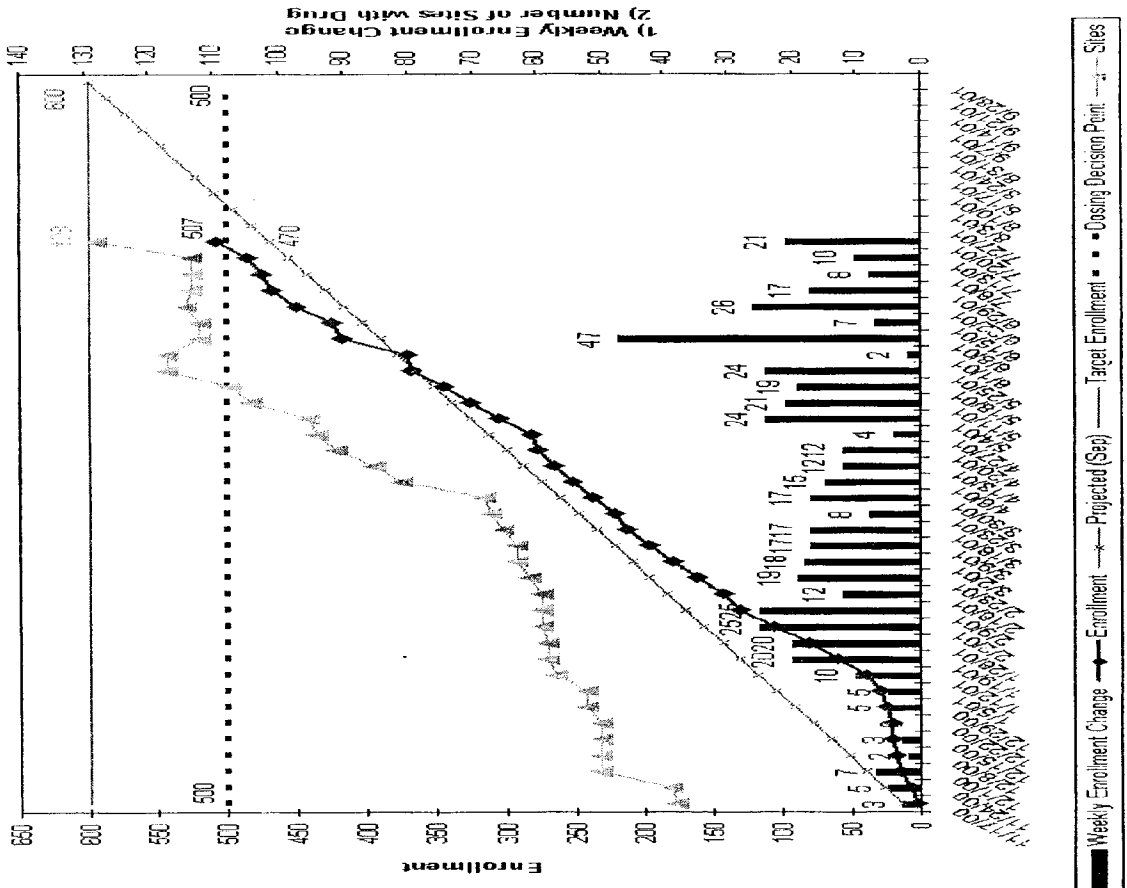
Current Clinical program

- AECB
 - Pivotal Studies at 150mg QD ongoing
- Pharyngitis
 - Pivotal Studies at 150mg QD ongoing
- CAP and Sinusitis Phase2/3 studies
 - 150mg QD vs. 150 mg BID
 - Collecting microbiological data

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M00-225 ABS Study (All Sites)
Acute Bacterial Sinusitis



Preliminary PP Clinical Response Blinded Data

| | Cure | Failure | Ind. | Total |
|-----------|-----------|---------|------|-------|
| CAP | 158 (92%) | 14 | 32 | 204 |
| Sinusitis | 230 (83%) | 46 | 21 | 297 |
| ABECB | 309 (84%) | 60 | 26 | 395 |
| Phary. | 362 (87%) | 55 | 30 | 447 |

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Six strategic alternatives were evaluated by the team on the basis of technical, regulatory and commercial attributes.

1. Complete current ABS & CAP dose-ranging trials and then make dose decision. (Use ABS & CAP dose-ranging data)
2. Complete only the ABS dose-ranging study and then make a dose decision for both ABS & CAP. (Use ABS dose-ranging data only)
3. Select the BID dose today for ABS & CAP Ph III pivotal. (Select BID today)
4. Select the QD dose today for ABS & CAP Ph III pivotal. (Select QD Today)
5. Develop BID in CAP & ABS for EU; Develop QD for US. (QD in the US & BID in the EU)
6. Expand the Phase III CAP program to allow for 3 arms per study – QD vs.. BID vs.. comparator. (Phase III 3-arm CAP & ABS pivotal). Variation: drop arm on result availability

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Four alternatives were shown to be not feasible due to regulatory and technical constraints (I).

- **“Select QD Today” and “QD in the US & BID in EU”:**
 - Both of these alternatives require that Phase III pivotal are initiated with the QD dose prior to the completion of the dose-ranging studies.
 - Given that Abbott sought out FDA approval for the current Phase III dose-ranging studies, there is a <10% probability that we would be permitted to proceed with the lower dose without supporting data.
 - In EU skepticism expressed at QD dose; could impact approvals of Phase III
- **“Phase III 3-arm CAP & ABS pivotal” variations thereof**
 - Without dropping an arm:
 - Increases numbers by 1/3
 - Defers decision to end of Phase 3
 - Risk of incongruity with results from 2nd study

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Four alternatives were shown to be not feasible due to regulatory and technical constraints (II).

- **Phase III 3-arm CAP & ABS pivotal” variations thereof**
 - Dropping arm when CAP data available
 - There is no precedent for the FDA allowing the dropping of an arm during Phase III in a pivotal. FDA might not sanction trial to start given dose trials ongoing.
 - Dropping arm will require scientific amendment, could potentially be refused by some authorities (EU)
 - Statistical challenges of randomizing block size, but not limiting; Statistical “hit”
- **Deferring dose decision to sinusitis data date (and variations)**
 - significant regulatory issues with splitting dose between CAP and sinusitis,
 - unless BID dose preferred choice..discussed later
 - extrapolating QD dose to CAP, but regulatory approval unlikely, although statistical and functionally feasible
 - early blind break , while statistically and functionally feasible has significant regulatory risk.

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The estimated NDA filing date and launch is impacted by the timing of the QD/BID dose decision.

| Dose Selection Strategy | Dose Decision Date | Phase III | | NDA Filing | Expected launch |
|---------------------------------|--------------------|-----------|--------|------------|-----------------|
| | | Start | Finish | | |
| Select BID Today | Jul 01 | Nov 01 | May 03 | Sep 03 | Winter 04 |
| Use ABS & CAP dose-ranging data | Mar 02 | Sep 02 | Oct 03 | Mar 04 | Winter 05 |

RTI is seasonal therefore launch tied to first winter after approval

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Key technical assumptions.

- Probability that ABT-773 achieves a resistance claim, given sufficient enrollment:
 - QD dose: 60%
 - BID dose: 80%
- Current dose-ranging studies:
 - Probability that ABS QD dose is <10% different from BID: 50%
 - Probability that CAP QD dose is <10% different from BID: 75%
- Phase III risk assessments:
 - Probability QD dose succeeds in ABS: 25%
 - This probability increases to 35% if dose-ranging shows statistical non-inferiority.
 - Probability BID dose succeeds in ABS: 65%
 - Probability QD dose succeeds in CAP: 65%
 - This probability increases to 75% if dose-ranging shows statistical non-inferiority.
 - Probability BID dose succeeds in CAP: 85%

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Key commercial assumptions.

- Base Peak Sales Forecast:
 - US: \$432MM
 - EU: \$295MM
- Impact of BID dosing:
 - US: 23% loss of share vs. QD (up to 50%)
 - EU: 21% loss of share vs. QD
- Impact of Ph IV QD line extension if BID dose is selected today:
 - US: 20% recovery of lost share
 - EU: 50% recovery of lost share
- Impact of launching with a resistance claim:
 - US: 32% increase in share
 - EU: 49% increase in share

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Key regulatory assumptions.

- CAP is critically important to product approval in both the EU and US.
- EU regulatory risk is high if either ABS or CAP fail to meet clinical endpoints.
- ABT-773 PK/PD data are most important for EU approval. FDA more likely to be convinced by clinical cure rates.
- A resistance claim significantly increases the probability of regulatory approval in both the US & EU.
- Given that FDA input was solicited for the current dose-ranging study, there is a very small probability that we would be permitted to proceed with a QD dose without supporting data (i.e. before ABS & CAP dose-ranging data are available).
- Selection of the 150 mg BID dose prior to completion of the dose-ranging data is likely to be acceptable to all regulatory agencies.

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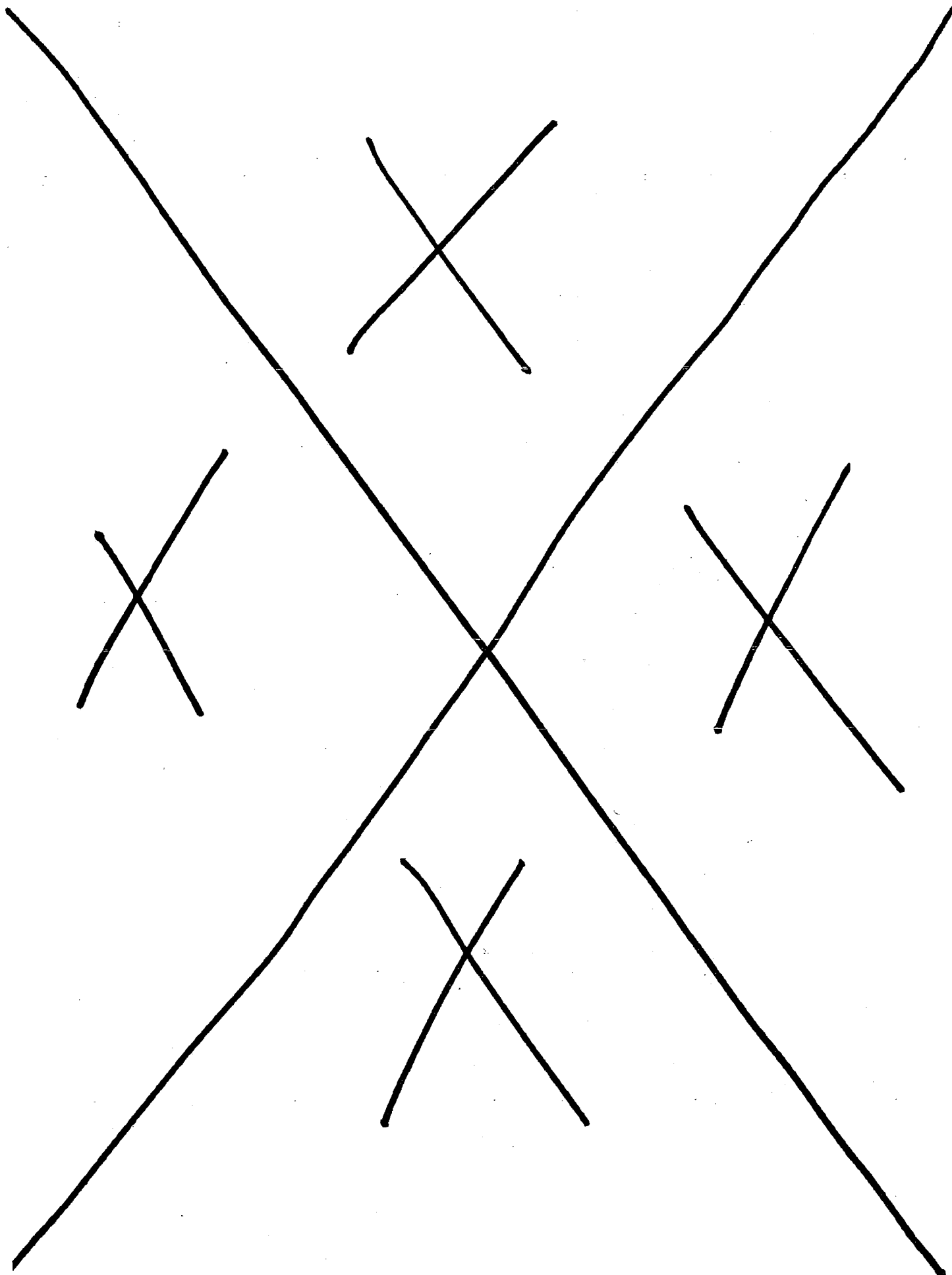
Selecting a BID dose today has a higher expected value than waiting for the dose-ranging data.

| Strategic Alternative | Expected Value (\$MM) | | |
|----------------------------|-----------------------|-----|-----|
| | US | EU | WW |
| Select BID Today | 137 | 202 | 339 |
| Wait for Dose-Ranging Data | 147 | 112 | 259 |

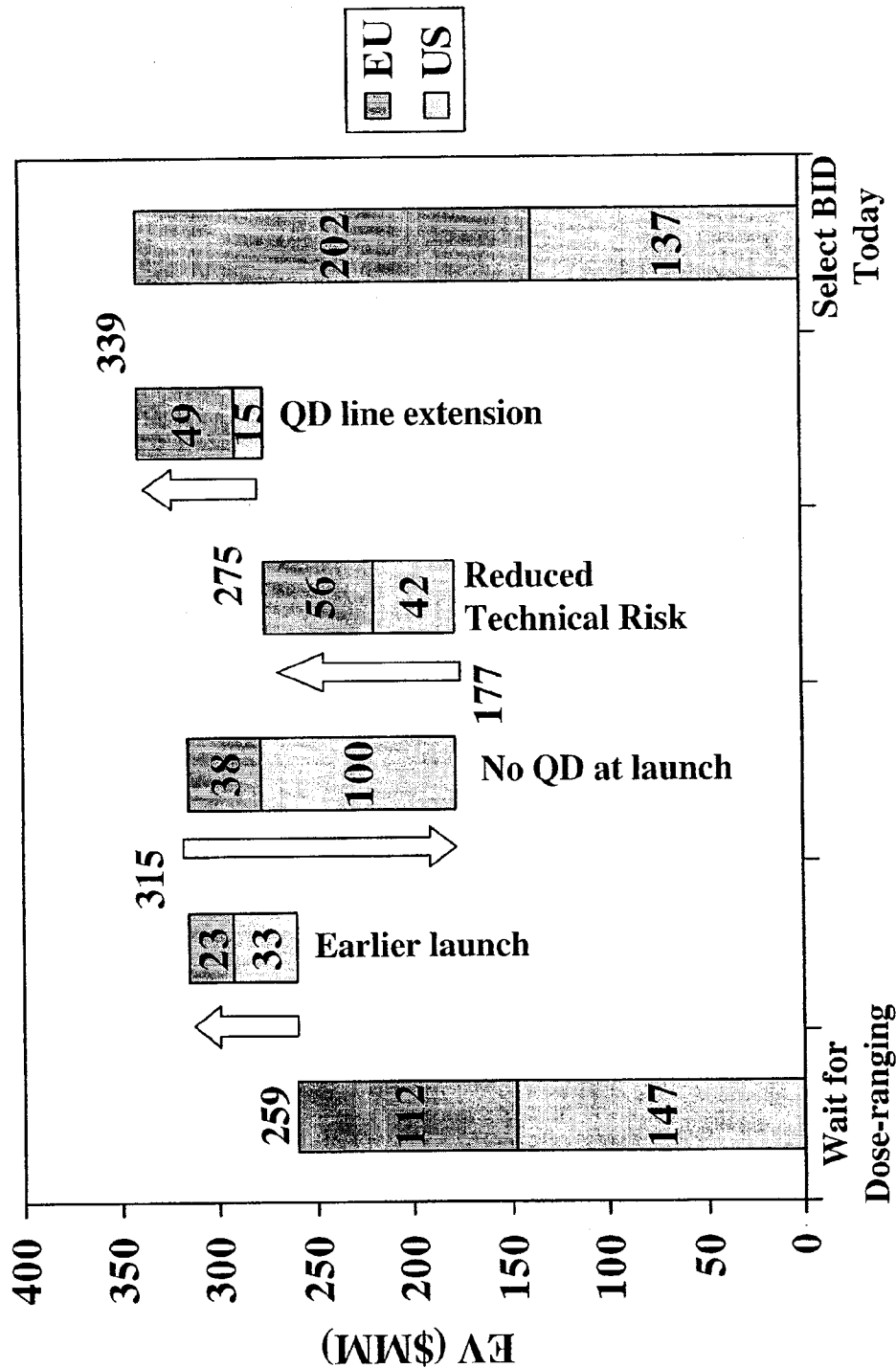
- The expected value of ABT-773 in the US is slightly increased by exploiting every opportunity for a QD dose:
 - The commercial penalty for BID dosing in the US is significant:
 - 23% loss of share if both CAP & ABS are BID.
 - 20% recovery of share with a post-launch QD line extension.
- The expected value of ABT-773 in the EU is maximized by pursuing the shortest possible path to market:
 - In the EU, the penalty for BID dosing is less severe:
 - 21% loss of share if CAP & ABS are BID.
 - However, 50% recovery of share with a post-launch QD line extension.

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The adverse commercial impact of selecting BID today is offset by reduced technical risk, accelerated timelines, and the option to follow with a QD line extension.



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Sensitivity to technical inputs.

- The base model shows that the dose-ranging data does not add incremental value over selecting BID today.
 - This is due the several factors, the two key ones being:
 - The assumption that the QD dose in ABS has only a 35% probability of technical success in Phase III, even when it is shown to be non-inferior (<10% difference from BID) during the dose-ranging study.
 - The US BID share loss due to BID is estimated to be around 23% (US market research forecast)
 - The key assumption differences that would lead to a conclusion to wait for the dose-ranging data are:
 - Belief that US BID share loss would be significant (~50%) AND
 - Somewhat higher probability of technical success with ABS (~45)

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Sensitivity to commercial inputs.

- In the US, waiting for the dose-ranging data has a slightly higher expected value than selecting BID today – this is due, in part, to:
 - The adverse commercial impact of the BID dose (23% loss of share).
 - Waiting for the dose-ranging data has higher value for all assessments greater than a 22% loss of share due to BID dosing.
 - Base case assumes 23% share loss based on market research.
 - US Marketing believes share loss could be as high as 50% at which point either strategy has equivalent worldwide expected value.
 - A Ph IV QD line extension is expected to recover only 20% of the lost share.
 - Selecting BID today is warranted only if more than 30% of lost share can be recovered with a Ph IV QD line extension (within two years of launch).
 - However, the share recovery must be significantly higher if the initial impact of BID dosing is –50%.
- In the EU, selecting BID today has a higher value:
 - The impact of launching with a BID dose (21% share loss) is mitigated by the QD line extension which can recover up to 50% of lost share.
 - Initial share loss can be as high as 60% before choosing to wait for dose-ranging data.

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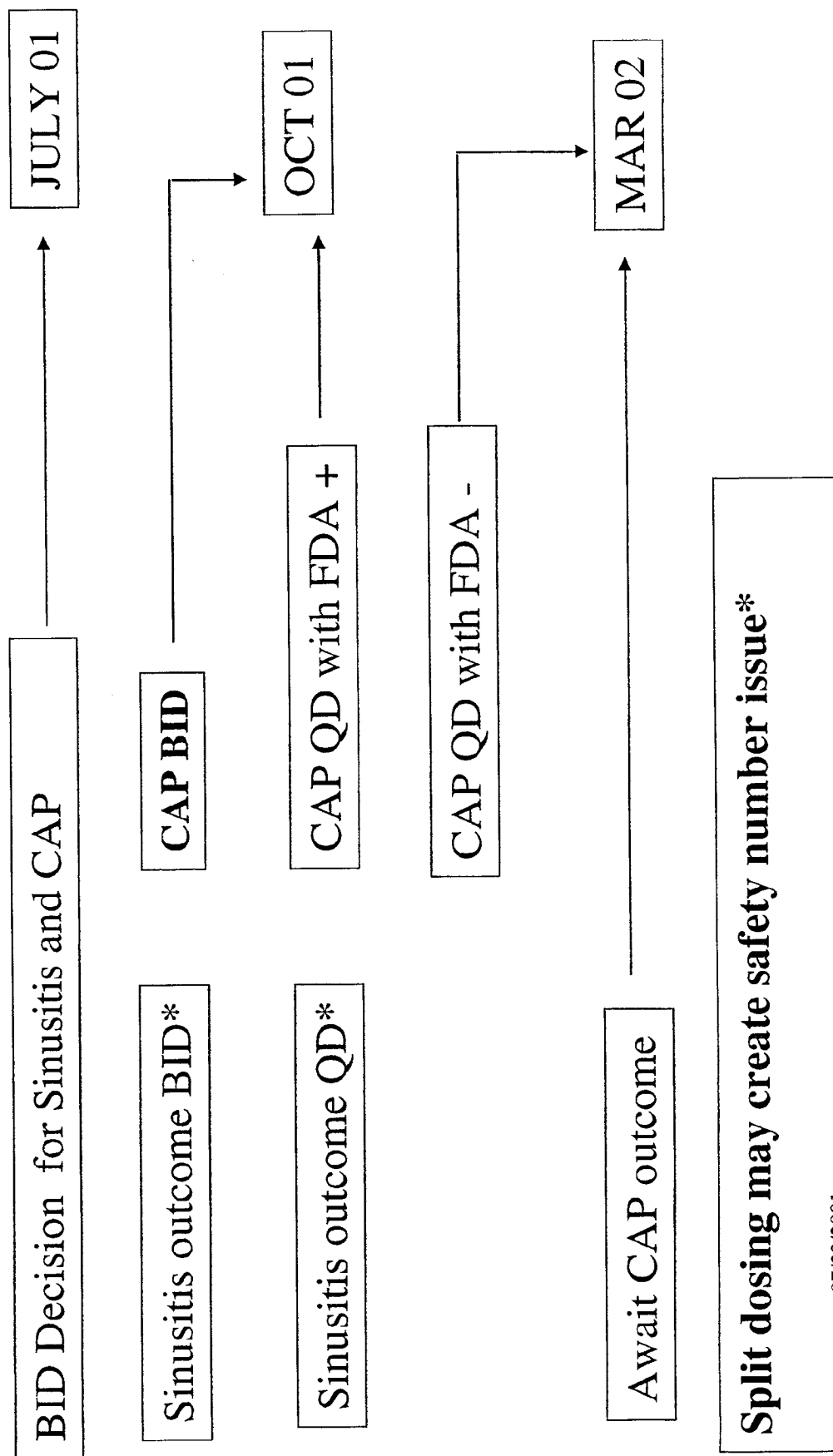
Key conclusions.

- The expected value of selecting the BID dose today exceeds the value of waiting for the dose-ranging data.
 - The earlier launch date, reduced technical risk, and option to pursue a Ph IV QD line extension outweigh the adverse commercial impact of launching at the BID dose.
- A favorable outcome for the QD dose in the dose-ranging study does not significantly increase the probability of technical success in Phase III.

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Timing of Dose decision



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Criteria for QD dose decision

Difference between QD and BID

- Analysis plan as in protocol
 - Cure rate in ITT and PP population meets confidence interval criteria
 - Efficacy in bacteriologically evaluable population is not statistically different between the 2 groups
 - Pathogen eradication rates are not statistically different between the 2 groups
- Statistically rigorous sanity check
 - Observed difference in clinical cure rate of QD vs. BID does not exceed X %

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Preliminary PP Clinical Response Blinded Data

| | Cure | Failure | Ind. | Total |
|-----------|-----------|---------|------|-------|
| CAP | 158 (92%) | 14 | 32 | 204 |
| Sinusitis | 230 (83%) | 46 | 21 | 297 |
| ABECB | 309 (84%) | 60 | 26 | 395 |
| Phary. | 362 (87%) | 55 | 30 | 447 |

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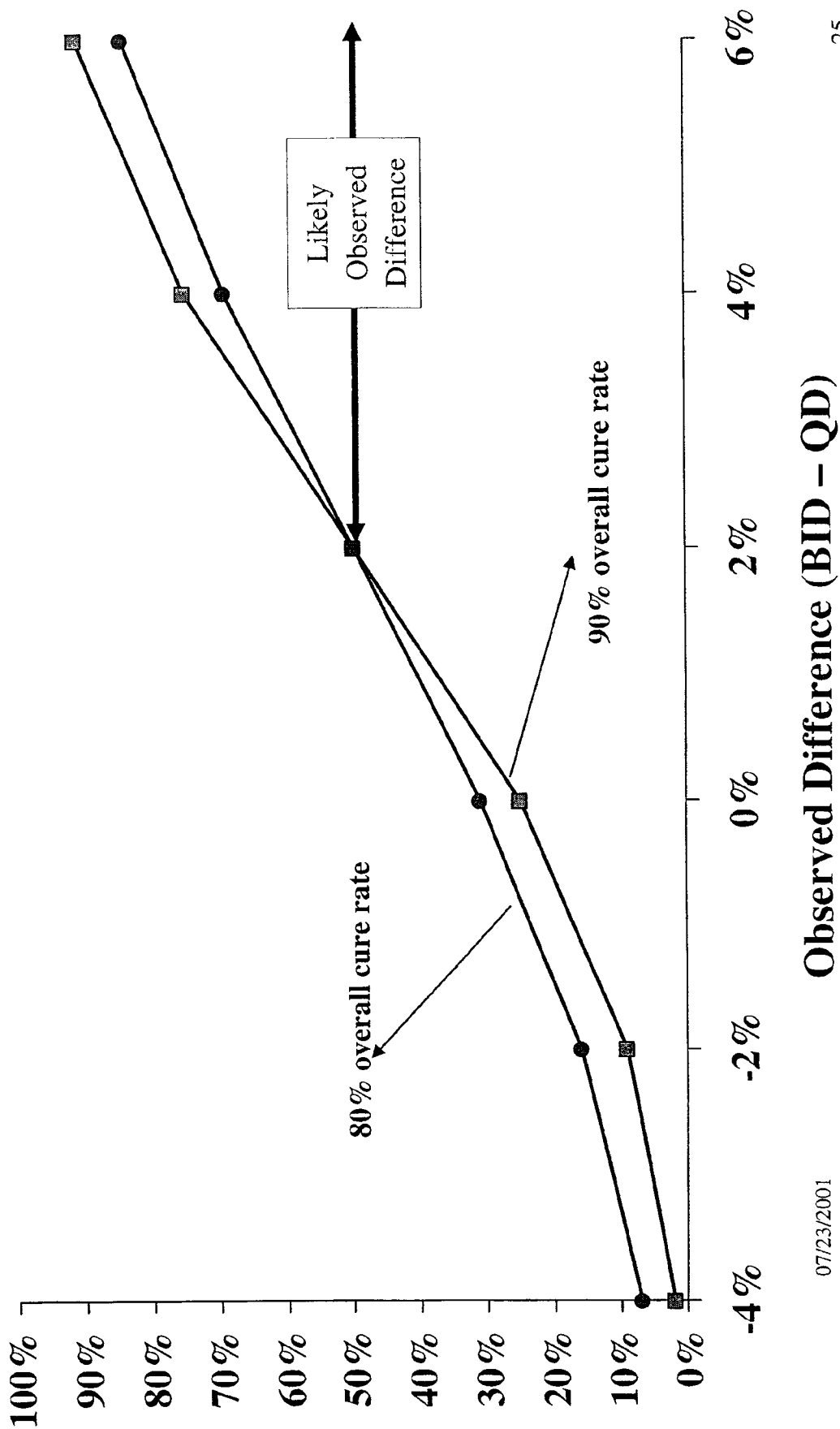
Power to Demonstrate Equivalence in a Phase 3 Trial

| | Cure Rate 90% | | | Cure Rate 85% | | | Cure Rate 80% | | |
|---------------|------------------|-----|------|------------------|-----|------|------------------|-----|-----|
| | 500 | 660 | 750* | 500 | 660 | 750* | 500 | 660 | 70* |
| True Diff. | | | | | | | | | |
| 0% | 92% | 97% | 97% | 80% | 90% | 90% | 71% | 82% | 82% |
| 2% | 73% | 84% | 85% | 59% | 67% | 72% | 50% | 62% | 63% |
| 4% | 46% | 57% | 59% | 36% | 42% | 47% | 31% | 38% | 39% |

* 2:1 ratio.
& Assuming 80% evaluability.

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Probability that True Difference is Greater Than 2% (N=500, 80% Evaluability)



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Power and Sample Size

| | Observed Ph. II ABT-773 Cure Rate | | | | | Expected Ph. III Comparator Cure Rate | Likely Comparator Cure Rate |
|-----|-----------------------------------|---------------|---------------|---------------|---------------|------------------------------------------------|-----------------------------------|
| | 90% | 87% | 85% | 83% | 80% | | |
| 90% | 97% N=354 | 71% N=814 | 41% N=1708 | 17% N=5039 | 3% IFN. | | |
| 87% | >99% N=236 | 93% N=445 | 75% N=739 | 49% N=1386 | 15% N=5955 | | |
| 85% | >99% N=190 | 98% N=329 | 90% N=501 | 71% N=824 | 33% N=2257 | | |
| 83% | >99% N=158 | >99% N=255 | 96% N=366 | 86% N=554 | 54% N=1206 | | |
| 80% | >99% N=124 | >99% N=186 | >99% N=251 | 97% N=350 | 82% N=629 | | |

Power is based on 660 patients with 1:1 ratio and 80% availability
 Sample size is based on 80% power and 80% evaluability and 1:1 ratio

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ABT 773 R&D Costs: Tablet

| Option | 2001 Budget | 2001 Var. | Total | Total Var. |
|-------------------------|-------------|-----------|-------|------------|
| Current R&D Cost | 88.5 | | 149.8 | |
| BID today | 87.0 | 1.5 | 166.2 | (16.4) |
| Wait for ABS & CAP data | 82.0 | 6.5 | 172.0 | (22.2) |

Additional costs due to:

- Increased patient numbers 500 patients
- Additional enrollment months/CRO time and resources
- Additional countries/sites

Current Year Additional Costs:

- QT, Pediatric and Japan - \$4.5MM

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Backups

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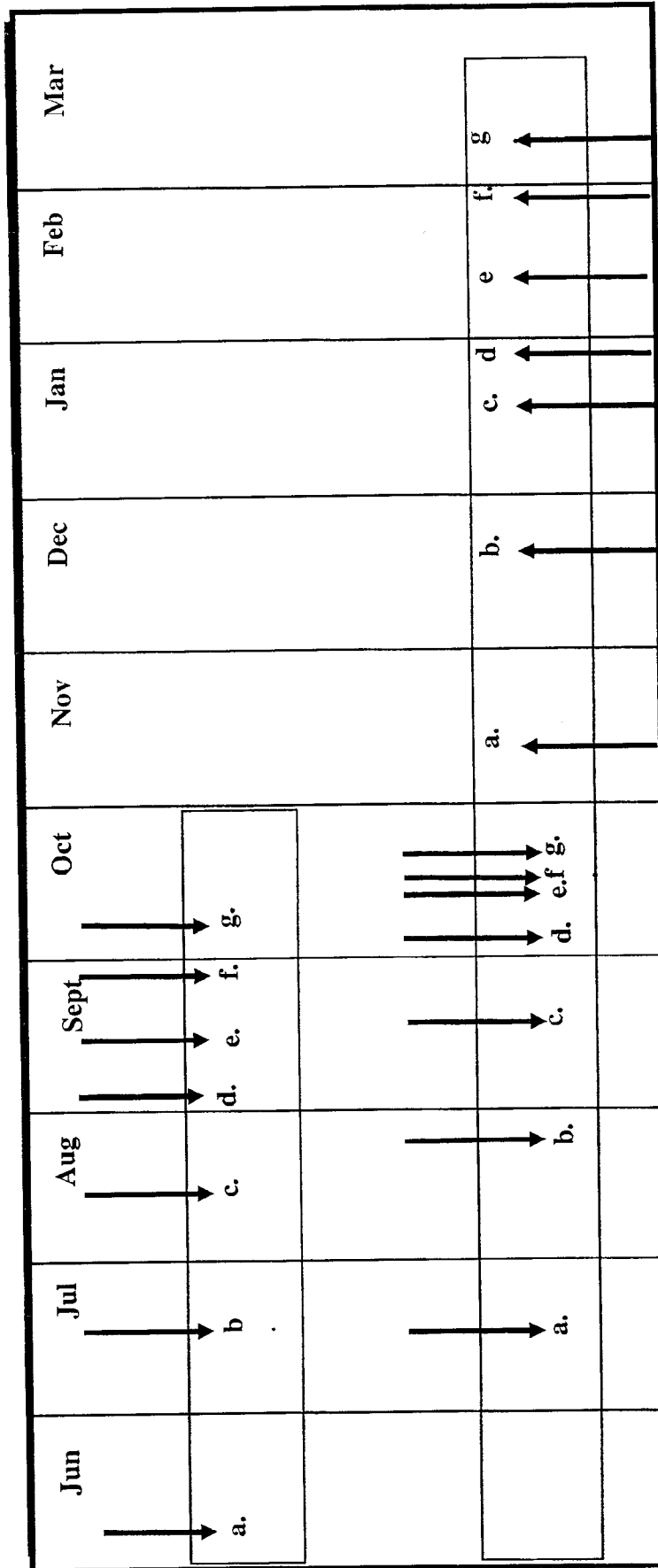
Potential Tactics to optimize delayed program timelines

- Ask FDA if we can extrapolate sinusitis data to CAP
 - Low probability given a trial is ongoing
- Ask FDA to unblind CAP data at 350 patients
 - may jeopardize support for AECB 150mg QD dose;
 - risk of excessive statistical penalty if completion also required;
 - if data analysis possible by Sept, answer from FDA in Dec has limited positive impact on timelines
 - risk of FDA requesting ITT instead of PP
- 3 arm study with option to truncate 1 arm
 - No regulatory precedent;
 - statistical risk
 - Low probability of ethics approval
- Continue accrual in existing CAP to reduce burden on Phase3 program.

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Start of Ph3 trials and filing dates dependant on dose decision timeline.

M00-225: Sinusitis 150 mg QD vs.. 150 mg BID M00-219: CAP 150 mg QD vs.. 150 mg BID



a. pts enrolled b. pts completed c. CRF in house d. queries resolved
e. final classification f. potential blind break g. dose decision

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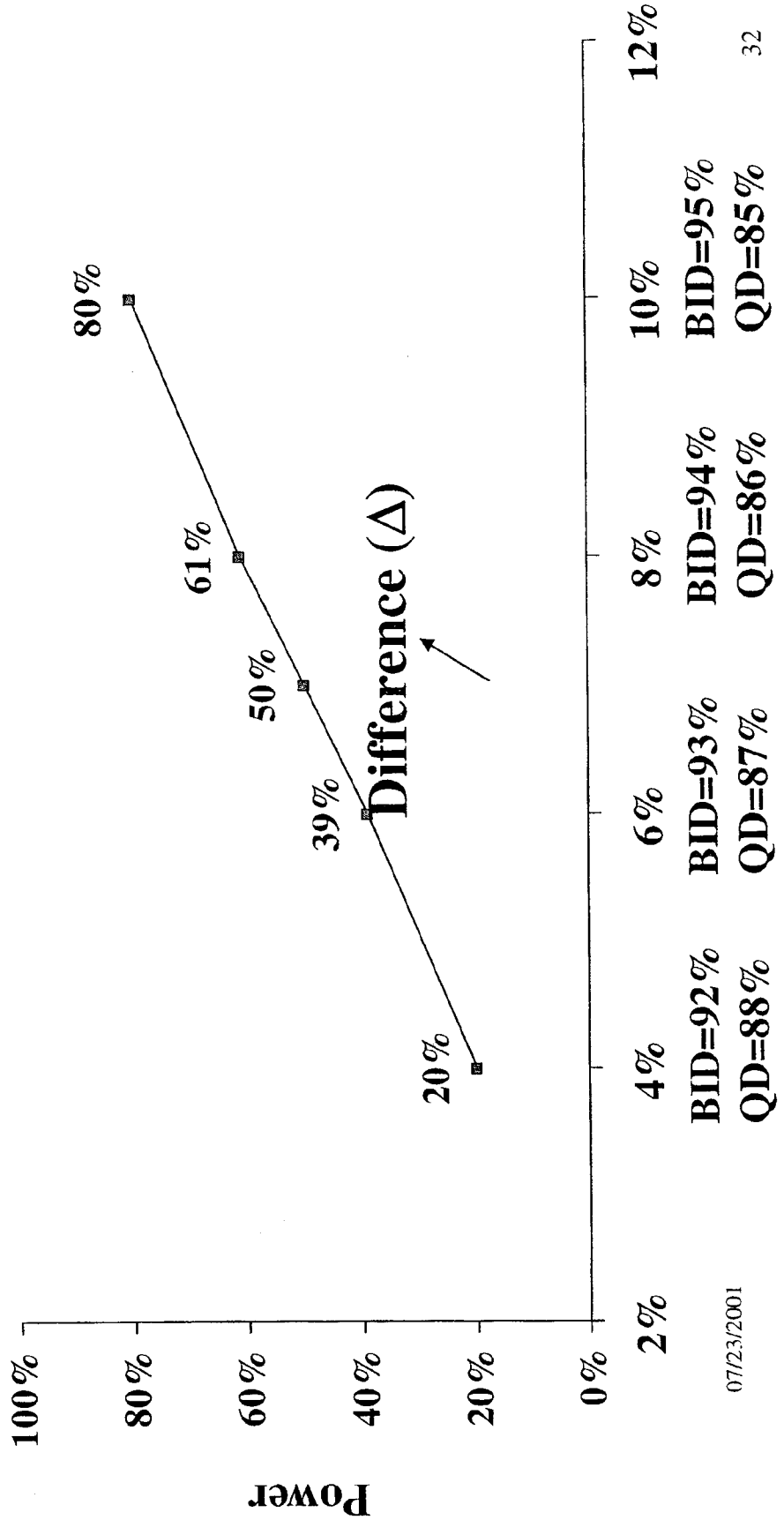
Current Clinical program

- AECB (Pivotal Studies at 150mg QD ongoing)
- Pharyngitis (Pivotal Studies at 150mg QD ongoing)
- CAP and Sinusitis (150mg QD vs. 150 mg BID)
 - Will support AECB at 150mg QD if equivalent
 - Will contribute to microbiologic data (including resistant pathogens) to meet regulatory requirements.
 - Will contribute to safety database.
- Making the dose decision today has a significant impact on program

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Power to Detect $\Delta\%$ Difference with 90% Overall Cure Rate (N=350, 80% Evaluability)



Dose Decision Outcome

Bid Dose Decision for Sinusitis

Extrapolate BID to CAP

- Regulatory default position for CAP
- Supports potential safety numbers at upper dose

QD Dose Decision for Sinusitis

Need regulatory agreement - 2+ months for FDA

- EU will default to approval/not protocols (Risk)
- Technical probability will work clinical cure in CAP
- Commercial defaults to QD

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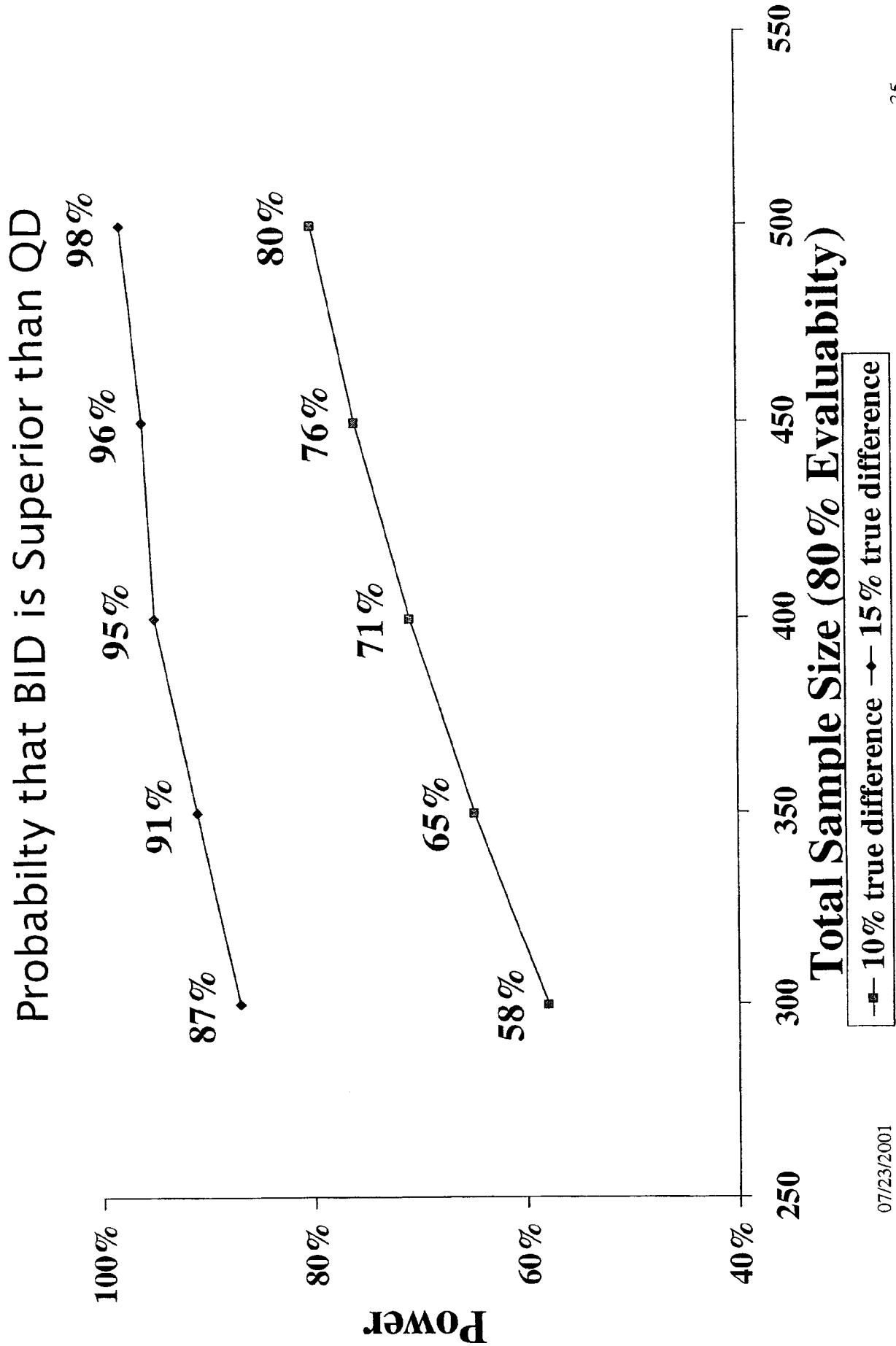
33

QD Dose Is Equivalent to BID Dose

- At least 90% overall clinical cure rate is observed for CAP study up to now (approximately 200 patients)
- Historically, clinical cure rate for antimicrobial is around 90%, which implies that it is unlikely two dose regimens are different
- Assuming 90% cure rate for both dose regimens and 80% evalubility, 350 total patients will provide 80% power to demonstrate equivalence per FDA and CPMP equivalent rule (10% rule)

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ABT 773 R&D Costs: Other Programs

| OTHER PROGRAM COSTS | 2001 | 2002 | 2003 | 2004-05 | TOTAL |
|------------------------------|---------------|-------------|-------------|----------------|--------------|
| IV FORMULATION | 0.5 funded | 9.2 | 9.8 | 3.9 | 23.4 |
| PEDIATRIC | 1.5 | 9.0 | 21.5 | 22.4 | 54.4 |
| JAPAN DEVELOPMENT | 1.0 | 2.0 | TBD | TBD | TBD |
| QT STUDY/EKG RE-READS | 2.0 | | | | |

Pediatric program needs to be at least up to Phase2 to get adult indication (\$10.5MM)

IV program offers significant commercial upside with breakeven in 1 year

QT study and reread ECG's not optional for Adult dose approval.

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Potential Time or Cost Savings

- CMC activities to be optimized
- 3rd study in non-competing countries to cut timeline by allowing only 500 not(750)(patients in EU CAP
- Continue enrollment in all sites until ethics approval for pivotal may shorten timeline.
- Given EKG QT study ask FDA to lessen load of EKG's in pivotal will reduce costs.
- Ask Regulatory authorities to consider IV Phase 3 step down program to increase numbers.

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Phase II Clinicals
Combined ABECB, CAP, ABS
Clinical Response

| | 150 mg | 300 mg | 600 mg |
|----------------------------|----------------------|----------------------|----------------------|
| Clin and Bact. Eval | 84% (42/50) | 90% (103/115) | 88% (106/120) |
| Clin Eval | 88% (168/193) | 88% (247/279) | 81% (216/265) |
| ITT | 83% (176/211) | 82% (259/314) | 75% (230/305) |

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Critical timeline to filing Using Sinusitis data alone timeline

| | Jun | Jul | Aug | Sep | Oct | Nov | Dec |
|------------------------------|-----|-----|-----|-----|-----|-----|-----|
| Phase 3 CAP studies complete | | | | | | | |
| Final study classifications | ■ | | | | | | |
| Database Lock | ■ | | | | | | |
| Blind Break | | ■ | | | | | |
| Statistical analysis | | | ■ | | | | |
| Reviewed final CSR | | | ■ | ■ | | | |
| NDA preparation | | | | ■ | ■ | | |
| CPMP Part2 | | | | ■ | ■ | | |
| Internal Reviews | | | | | ■ | ■ | |
| E-Filing | | | | | | ■ | ■ |

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Critical timeline to filing Using BID today timeline

| | Apr | May | Jun | Jul | Aug | Sep | Oct |
|------------------------------|-----|-----|-----|-----|-----|-----|-----|
| Phase 3 CAP studies complete | ■ | | | | | | |
| Final study classifications | ■ | | | | | | |
| Database Lock | | ■ | | | | | |
| Blind Break | | ■ | | | | | |
| Statistical analysis | | | ■ | | | | |
| Reviewed final CSR | | | ■ | | | | |
| NDA preparation | | | | ■ | ■ | | |
| CPMP Part2 | | | | ■ | ■ | | |
| Internal Reviews | | | | | | ■ | |
| E-Filing | | | | | | | ■ |

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Phase II Clinicals
Combined ABECB, CAP, ABS
Bacteriological Response

Clinically and Bacteriologically Evaluable

| | 150mg | 300mg | 600mg |
|-----------------------|-------------|-------------|-------------|
| <i>S. pneumoniae</i> | 87% (13/15) | 91% (30/33) | 91% (29/32) |
| <i>M. catarrhalis</i> | 84% (16/19) | 84% (21/25) | 84% (16/19) |
| <i>H. influenzae</i> | 87% (20/23) | 94% (33/35) | 77% (37/48) |
| Overall | 86% (49/57) | 90% (84/93) | 83% (82/99) |

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Phase II Clinicals
Combined ABECB, CAP, ABS

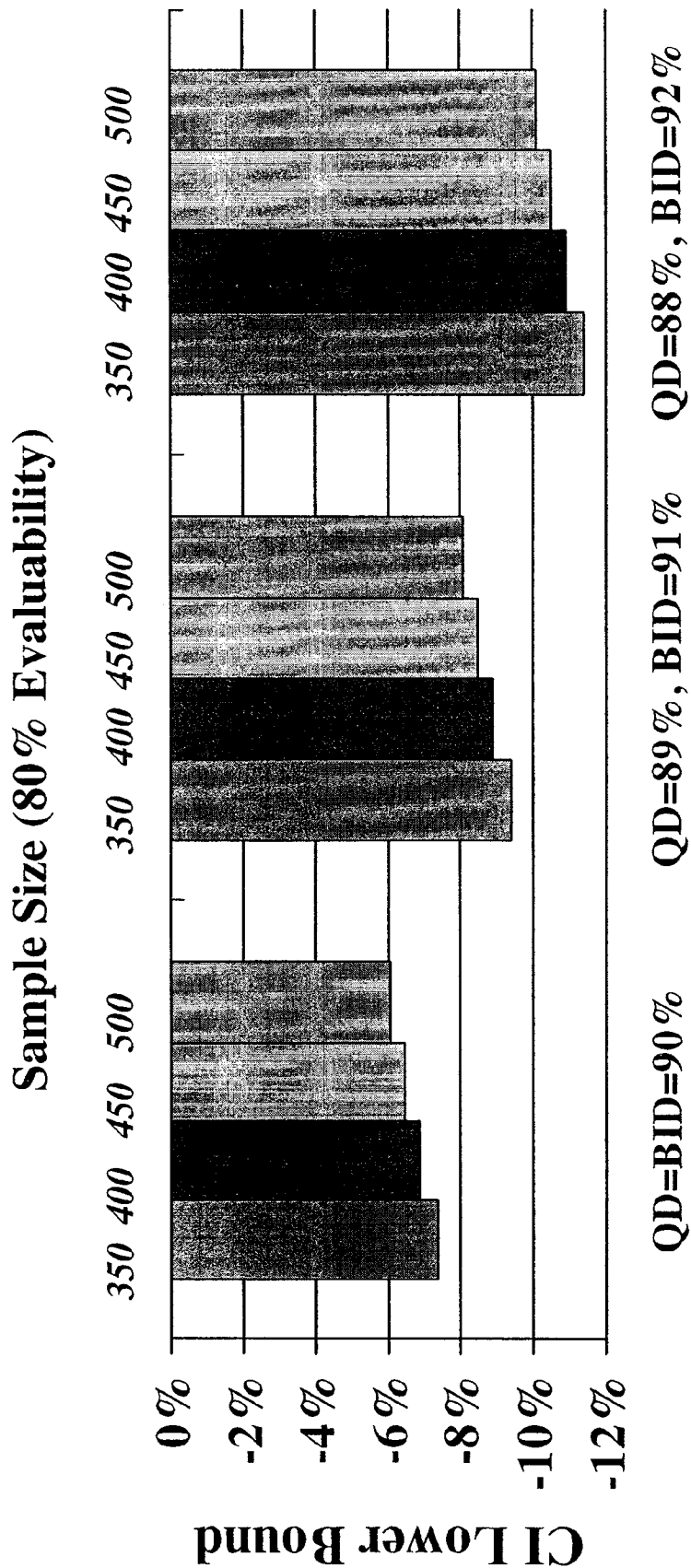
All Adverse Events

| | 150 mg | 300 mg | 600 mg |
|-------------------------|--------------|--------------|--------------|
| GI and Taste | | | |
| Taste Perversion | 4% (8/223) | 17% (55/322) | 27% (87/318) |
| Diarrhea | 10% (22/223) | 11% (34/322) | 19% (60/318) |
| Nausea | 5% (12/223) | 12% (40/322) | 26% (83/318) |
| Vomiting | 2% (4/223) | 6% (19/322) | 14% (44/318) |

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Two Sided 95% Lower Confidence Bound of Difference (150 QD – 150 BID)

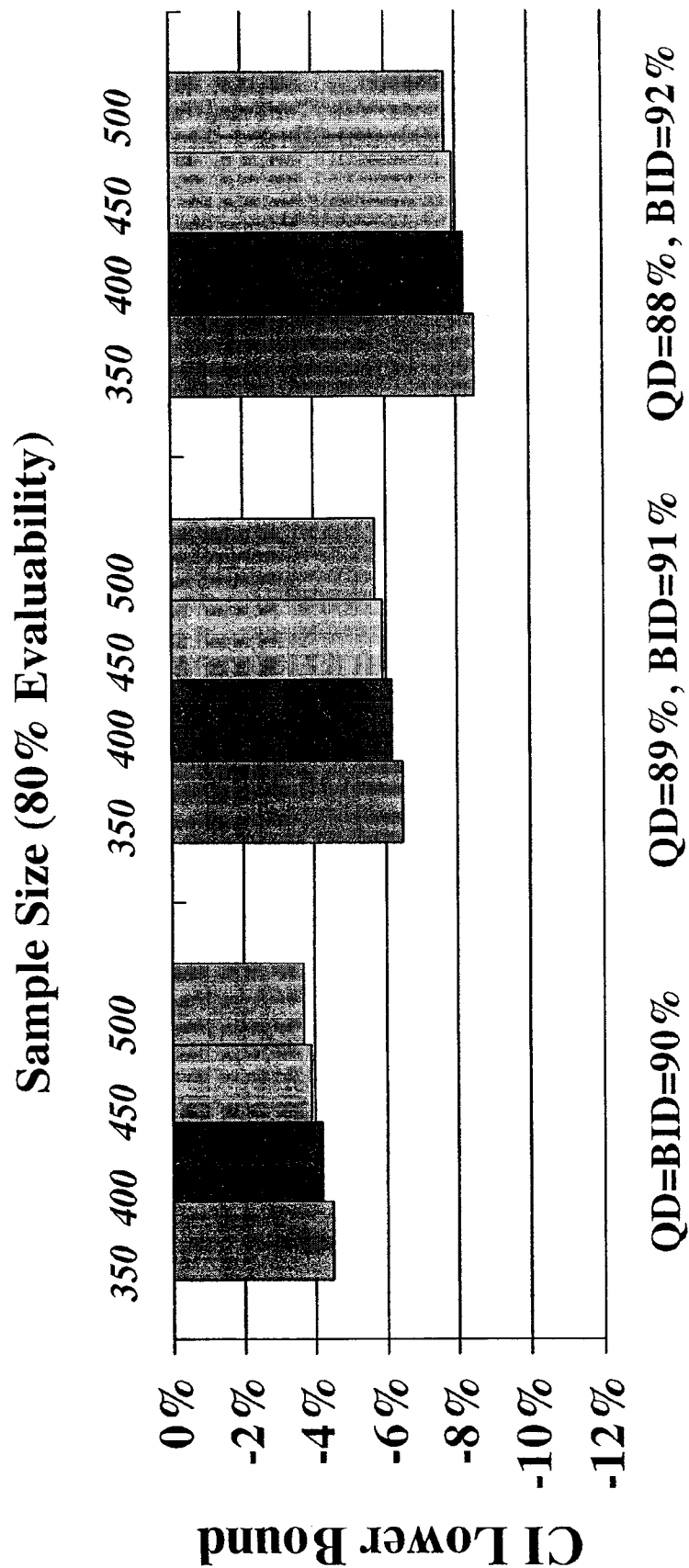


Observed Cure Rates

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Two Sided 75% Lower Confidence Bound of Difference (150 QD – 150 BID)



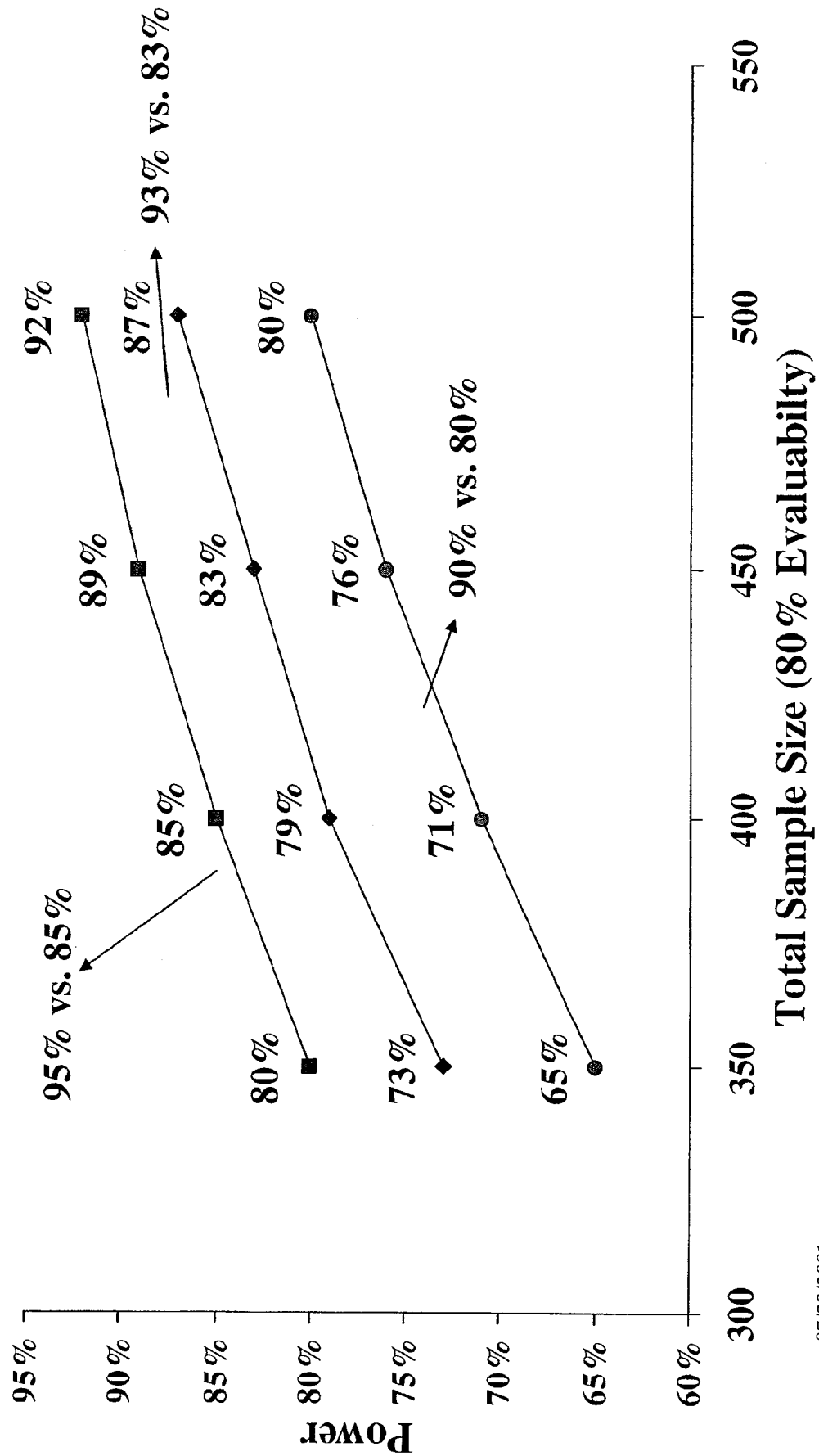
Observed Cure Rates

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Current Data supports a rational reason to justify unblinding CAP Data

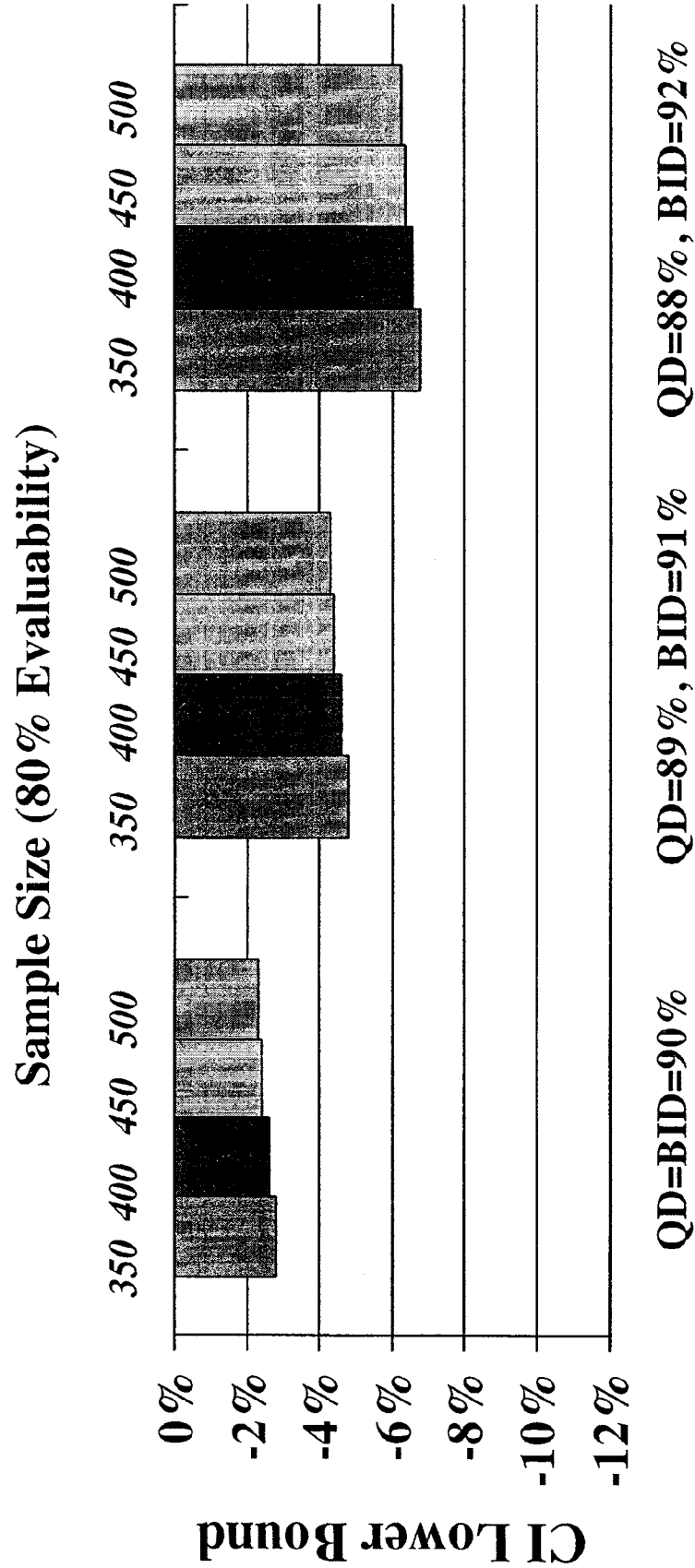
Power to Detect 10% Difference



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Two Sided 50% Lower Confidence Bound of Difference (150 QD – 150 BID)



Observed Cure Rates

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Pediatric - Summary

- FDA requires a Pediatric Development Program
 - Pediatric referral filed to FDA last year
 - Critical to show FDA compliance with regulation of Pediatric program for NDA (tablet) approval
- Two formulations were developed and tested in humans
 - Bio-equivalence was < 80% (~78%)
- Several tests to evaluate flavor:
 - ABT-773 between clarithromycin (worst) and azithromycin (best)
- Pediatric dose is estimated to be 2 times the final adult dose

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Pediatric - Summary

- Revised pediatric program:
 - Two or three new formulation under development
 - Dose will be adjusted to achieve desire plasma concentrations

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Pediatric Development Plan

Phase 1:

- 1- Single dose bio study:
 - 2 or 3 pediatric and reference formulations (IR-E)
- 2- Open IND with the following Multiple dose study:
 - pediatric selected formulation and reference (IR-E)
 - 300 mg QD for 5 days

Phase 2:

- 1- Otitis Media study versus Upper Resp Tract Infect study (otitis and pharyngitis):
 - a. Children 1 to 12 years of age
 - b. Three doses: 2.5, 5, 10 mg/kg/d (lower higher dose to 7.5 mg/kg)
 - c. Otitis media with double tap and middle ear fluid concentrations
 - d. Plasma samples
 - e. Maximum dose: 400 mg day

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Pediatric Development Plan

- Go/No go
- Phase 3:
3 studies:

Otitis media

Pneumonia (IV?/?/PO)

Pharyngitis

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BID today Start Pivotal Trials

| Activities | July | Aug. | Sept. | Oct. | Nov. |
|-----------------------------------------|-------------|-------------|-------------|-------------|---------------------------------------------|
| Select CRO | <div></div> | | | | |
| Draft Protocol | <div></div> | | | | |
| Protocol Sign Off | | <div></div> | | | |
| Prep FDA submission | | <div></div> | | | |
| FDA submission/approval CAP blind break | | <div></div> | <div></div> | | |
| Dose Decision + 1 Day | | | <div></div> | <div></div> | |
| Reg. Docs. Approved | | | <div></div> | <div></div> | |
| IRB approvals | | | <div></div> | <div></div> | |
| Drug Packaging/both options | <div></div> | | <div></div> | | |
| Site initiations | | | <div></div> | <div></div> | |
| First Patient enrolled US/EU + 6 | | | | | <div></div> <div>CAP & Sinusitis*</div> |

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Pediatric – Summary: Issues

1. ABT-773 presentation 2 concentrations (example: 150 mg/5mL and 300 mg/mL) vs.. 1 concentration (either)
2. Blinding for phase 2 studies
3. Need External Safety Review for Phase 2 (tolerability of higher dose)
4. Final ages: 6 months up 12 years
5. Final dose selection will be impacted by the dose selection from adults (BID vs.. QD)

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SAE Summary Phase 2b

| | | |
|---------------------|----------|------|
| • M99-048 AECEB | (6/384) | 2% |
| • M99-053 Sinusitis | (3/292) | 1% |
| • M99-054 CAP | (14/187) | 7.5% |
| • Total | (23/863) | 3% * |

*2 Expedited Reports

07/23/2001

SAE Summary Phase 3 (IND Studies)

| | | |
|-----------------------|-----------|-------|
| • M00-216 AECB | (15/456) | 3.3% |
| • M00-219 CAP | (21/343) | 6.1% |
| • M00-223 Pharyngitis | (5/522) | 1.0% |
| • M00-225 Sinusitis | (4/485) | 0.8% |
| • Total | (45/1805) | 2.45% |

* As of July 08, 2001

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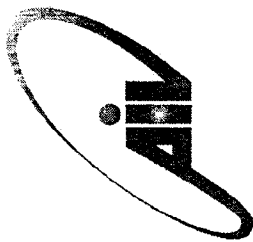
Pregnancies

- M00-223
 - 3 SUBJECTS*
- M00-225
 - 2 SUBJECT
- Total 5 pregnancies

* One subject had an elective abortion

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*Abbott Laboratories
Anti Infective Venture
Global Pharmaceutical Research & Development*

Stan Bukofzer, MD
Head, Anti Infective Venture
July 25, 2001

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- Agreed on best dose probability

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Potential Implications of 150mg QD vs. 150mg BID put in slide of pros and cons

- Having embarked on a dose deficiency trial, we might default US to await outcome
- Based on PK/PD profile, skepticism by medical advisors and regulatory authorities as to success of QD dose, however, commercial favor QD dosing
- Concern that QD dose might encourage emergence of resistance
- Split dosing will go against regulatory mainstream (EU > US) and could adversely affect safety numbers at 150 mg BD dose
- ABS data cannot necessarily be used to extrapolate to CAP dose for EU and possibly for US

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Power to Demonstrate Equivalence in a Phase 3 Trial

| | Cure Rate 90% | | | Cure Rate 85% | | | Cure Rate 80% | | |
|---------------|------------------|-----|------|------------------|-----|------|------------------|-----|------|
| | 500 | 660 | 750* | 500 | 660 | 750* | 500 | 660 | 750* |
| True Diff. | | | | | | | | | |
| 0% | 92% | 97% | 97% | 80% | 90% | 90% | 71% | 82% | 82% |
| 2% | 73% | 84% | 85% | 59% | 67% | 72% | 50% | 62% | 63% |
| 4% | 46% | 57% | 59% | 36% | 42% | 47% | 31% | 38% | 39% |

* 2:1 ratio.
& Assuming 80% evaluability.

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Preliminary Phase III Blinded Data All Adverse Events

| | Taste | Nausea | Diarrhea | Vomiting |
|--------------------------------------------|----------------------|----------------------|----------------------|----------------------|
| Bronchitis 150 QD vs. AZI | 0.7% (1/130) | 3.8% (5/130) | 7.6% (10/130) | 0.7% (1/130) |
| CAP 150 QD or 150 BID | 5.1% (3/58) | 8.6% (5/58) | 5.1% (3/58) | 6.8% (4/58) |
| Pharyngitis 150 QD vs. Pen | 2.2% (3/135) | 14.0% (19/135) | 6.6% (9/135) | 6.6% (9/135) |
| Sinusitis 150 QD or 150 BID | 5.7% (7/122) | 9.8% (12/122) | 4.0% (5/122) | 3.2% (4/122) |
| TOTAL | 3.1% (14/445) | 9.2% (41/445) | 6.0% (27/445) | 4.0% (18/445) |

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Compares favorably to Clari and Ketek profiles

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Factors Affecting 150 mg QD Dose Selection

| For | Against |
|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| <ul style="list-style-type: none">• All subjects available for safety evaluation• Favorable results of CAP may be used to support bronchitis• ↓ risk of unfavorable tolerability profile• ↓ risk of QT effect | <ul style="list-style-type: none">• Based on Pk/PD modeling<ul style="list-style-type: none">– Higher Regulatory hurdle for demonstrating efficacy– Advisors skepticism of efficacy in CAP• Concern regarding emergence of resistance |

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Factors Affecting 150 mg BID Dose Selection

| For | Against |
|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| <ul style="list-style-type: none"> • Based on Pk/PD higher probability of achieving efficacy endpoints in Ph 3. • Greater acceptance by advisors and Reg agencies • Perception of less likelihood of BID resulting in emergence of resistance | <ul style="list-style-type: none"> • Potential for more unfavorable tolerability profile • Less safety margin for QT effect given potential CYP3A interactions • Some risk for adequacy of safety database in a two-dose program • Cost of goods higher |

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Tactics to maximize use of Winter '01

A BID decision today (both CAP/sinusitis)

A BID decision for CAP if Sinusitis is BID

If sinusitis QD with CAP QD based on 350 pats,

US requires FDA agreement to break blind.(end Sept) Data likely to favor CAP QD.

Downside risk of being told to wait on blind break

Delaying request to FDA until after sinusitis data will cause missed season

AI : QD decision requires national Agency meetings, but with supportive data unlikely to be time delaying. Will require starting at risk

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How to Make Dose Decision (Sinusitis)

If 10% difference, clinical cure per protocol → Decision

If less than 10% difference, consider clinical and bacterial cure as above

If more than 10% difference → Decision

If less then, >80% for one arm clinical and bacterial cure → Decision

If less than that, default to QD → Decision

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ABT-773 Preliminary Phase III Blinded Data
All Adverse Events

| | Taste | Nausea | Diarrhea | Vomiting | Headache |
|-----------------------------------|-------------------|----------------|-----------------|-------------------|------------------|
| Bronchitis 150 QD | 1.5% (6/397) | 3.5% (14/397) | 10.8% (43/397) | 0.7% (3/397) | 6.5% (26/397) |
| CAP 150 QD or 150 BID | 3.8% (8/207) | 6.2% (13/207) | 9.1% (19/207) | 5.3% (11/207) | 10.1% (21/207) |
| Pharyngitis 150 QD | 1.9% (9/453) | 8.8% (40/453) | 8.1% (37/453) | 4.4% (20/453) | 10.5% (48/453) |
| Sinusitis 150 QD or 150 BID | 5.2% (16/303) | 5.6% (17/303) | 5.6% (17/303) | 2.3% (7/303) | 5.6% (17/303) |
| TOTAL | 2.8% (39/1360) | 6.1% (84/1360) | 8.5% (116/1360) | 3.0%(41/1360) | 8.2% (112/1360) |
| 07/23/2001 | | | | | |

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Impact of CAP data on dose decision

- Imposes a delay to Sept 02 start of pivotal in CAP and sinusitis
- Predictive value of CAP data is essentially similar to sinusitis data (same dynamics of clinical trial data)
- Therefore no significant benefit due to delay in expected launch date
- No program cost advantage identified.

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DSG Backups

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Commercial impact of indication outcomes.

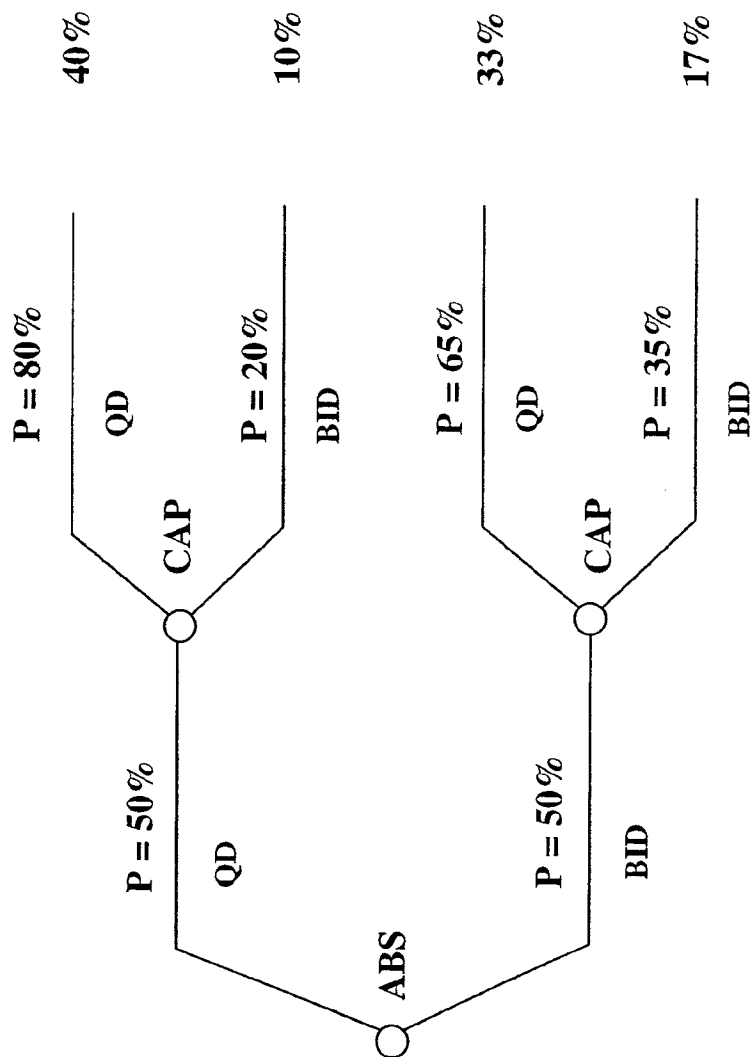
| Sinusitis | CAP | Phar | AECB | U.S. Share Impact | EU Share Impact |
|--------------------------------------------------|-----|------|------|-------------------|-----------------|
| Y | Y | Y | Y | 0% | 0% |
| N | Y | Y | Y | -20% | -20% |
| Y | Y | N | Y | -5% | -33% |
| N | Y | N | Y | -25% | -53% |
| N | Y | Y | N | -90% | -53% |
| N | Y | N | N | -90% | -87% |
| Y | Y | Y | N | -70% | -33% |
| Y | Y | N | N | -70% | -66% |
| CAP dosed BID instead of QD (others QD) | | | | | |
| Sinusitis dosed BID instead of QD (others QD) | | | | | |
| Both CAP/sinusitis dosed BID instead of QD | | | | | |
| Diarrhea rate decreases to 3% from 7% | | | | | |
| Diarrhea rate increases to 12% from 7% | | | | | |
| Taste perversion decreases to 2% from 4% | | | | | |
| Taste disturbance increases to 6% from 4% | | | | | |
| Both Pen-R and Mac-R claims are achieved | | | | | |
| Fracture of share recovered w/ QD line extension | | | | | |
| | | | | 32% | 49% |
| | | | | 20% | 50% |

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Asset: ABT-773
 Alternative: All
 Provided By: Joaquin Valdes,
 Stan Bukofzer
 Date: 5/23/01

*Probability of dose ranging showing that QD is not inferior to BID per protocol**

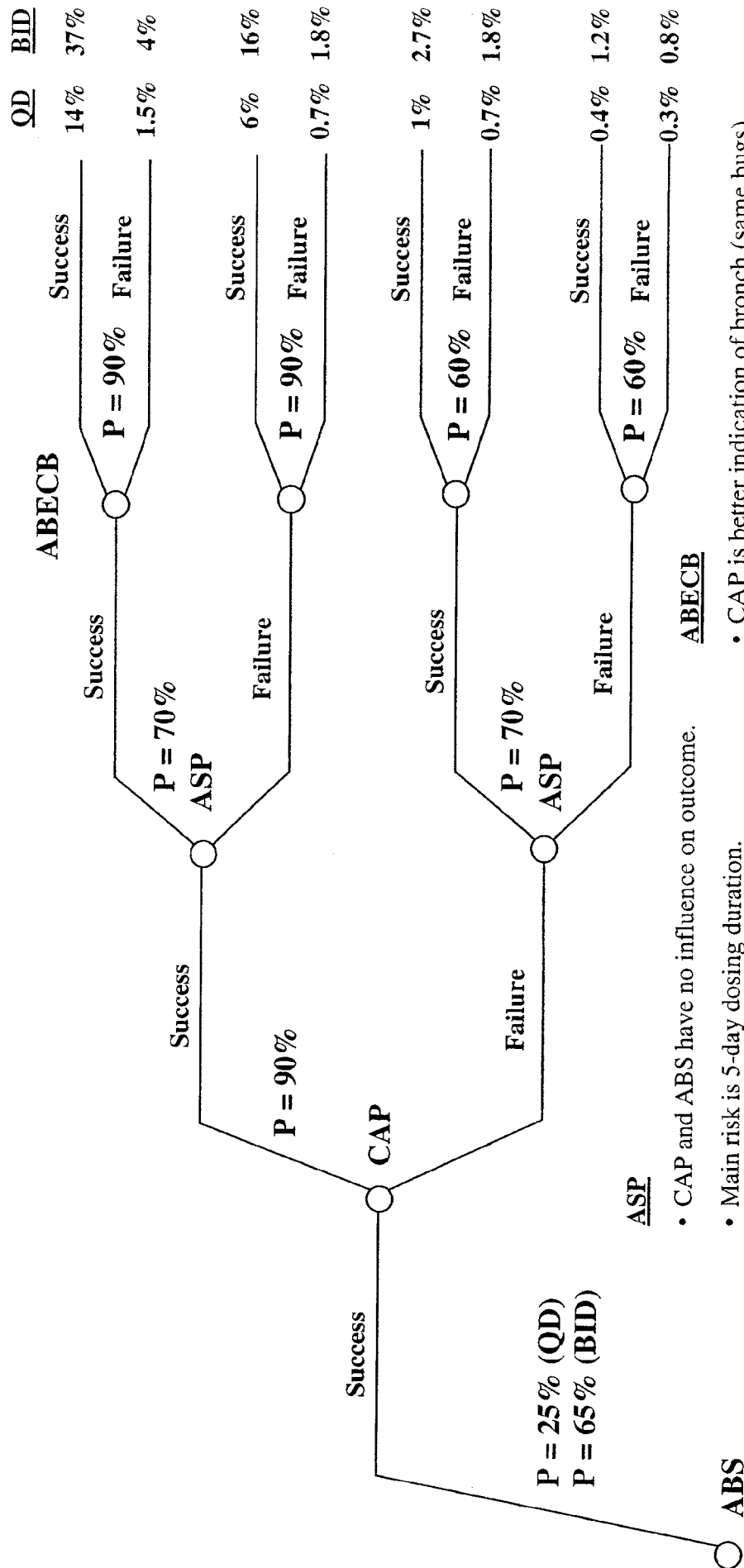


* QD is not greater than 10% less than BID at 80% power.

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Asset: ABT-773
 Alternative: All
 Provided By: Joaquin Valdes
 Date: 5/7/01

Efficacy: Co-variance between indications (ABS success)

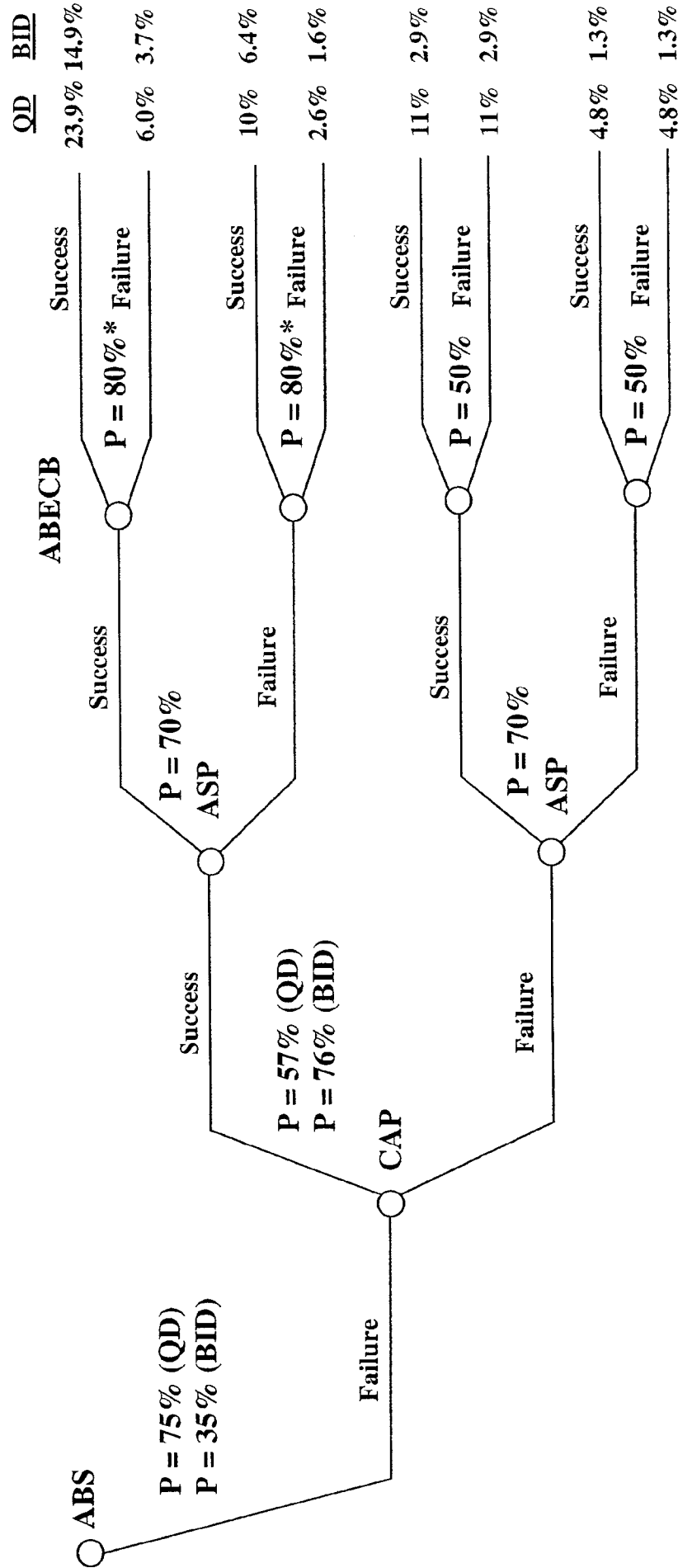


- CAP and ABS have no influence on outcome.
- Main risk is 5-day dosing duration.
- Endpoint is eradication rather than clinical cure.
- Only need to treat *S. pyogenes*
- CAP is better indication of branch (same bugs).
- CAP and ABECB are related.

07/23/2001

Asset: ABT-773
 Alternative: All
 Provided By: Joaquin Valdes
 Date: 5/7/01

Efficacy: Co-variance between indications (ABS failure)



* Calculations based on prior assessments
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Probabilities of regulatory approval (US).

| ABS | CAP | ASP | ABEC B | Regulatory Prob | |
|------------|-----|-----|-----------|-----------------------------|--------------------------------|
| | | | | With resistance claim | Without resistance claim |
| ✓ | ✓ | ✓ | ✓ | 0.95 | 0.90 |
| ✓ | ✓ | ✓ | | 0.85 | 0.80 |
| ✓ | ✓ | | ✓ | 0.95 | 0.90 |
| ✓ | ✓ | | | 0.85* | 0.75* |
| ✓ | | ✓ | ✓ | NA | 0.5 0.1 |
| ✓ | | ✓ | | NA | 0.1 0 |
| ✓ | | | ✓ | NA | 0.1 0 |
| ✓ | | | | NA | 0 0 |
| | ✓ | ✓ | ✓ | 0.85* | 0.75* |
| | ✓ | ✓ | | 0.50* | 0.25* |
| | ✓ | | ✓ | 0.70* | 0.40* |
| | ✓ | | | 0.50* | 0.25* |
| | | ✓ | ✓ | NA | 0 |
| | | ✓ | | NA | 0 |
| | | | ✓ | NA | 0 |
| 01/23/2001 | | | | NA | 0 |

- Assessments assume a perfectly clean safety database (except where indicated).
- All assessments assume 1st line treatment.
- Yellow boxes assume “clari-like” safety profile. Probabilities are significantly lower because the absence of CAP reduces the benefit/risk.
- Assessments with an asterisk (*) indicate outcomes where additional safety data will be needed for approval (to complete the safety database).
- Resistance was deemed approvable only in the case of CAP success (NA is shown where CAP fails).

Probabilities of regulatory approval (EU).

| ABS | CAP | ASP | ABEC B | Regulatory Prob | |
|-----|-----|-----|-----------|--------------------------------|-----------------------------|
| | | | | Without resistance claim | With resistance claim |
| ✓ | ✓ | ✓ | ✓ | 0.90 | 0.95 |
| ✓ | ✓ | ✓ | | 0.70 | 0.80 |
| ✓ | ✓ | | ✓ | 0.70 | 0.80 |
| ✓ | ✓ | | | 0.50 | 0.60 |
| ✓ | | ✓ | ✓ | 0.10 | 0.10 |
| ✓ | | ✓ | | 0.10 | 0.10 |
| ✓ | | | ✓ | 0.10 | 0.10 |
| ✓ | | | | 0.10 | 0.10 |
| | ✓ | ✓ | ✓ | 0.20 | 0.30 |
| | ✓ | ✓ | | 0.20 | 0.30 |
| | ✓ | | ✓ | 0.20 | 0.30 |
| | ✓ | | | 0.20 | 0.30 |
| | | ✓ | ✓ | 0.05 | 0.05 |
| | | ✓ | | 0.05 | 0.05 |
| | | | ✓ | 0.05 | 0.05 |
| | | | | 0 | 0 |

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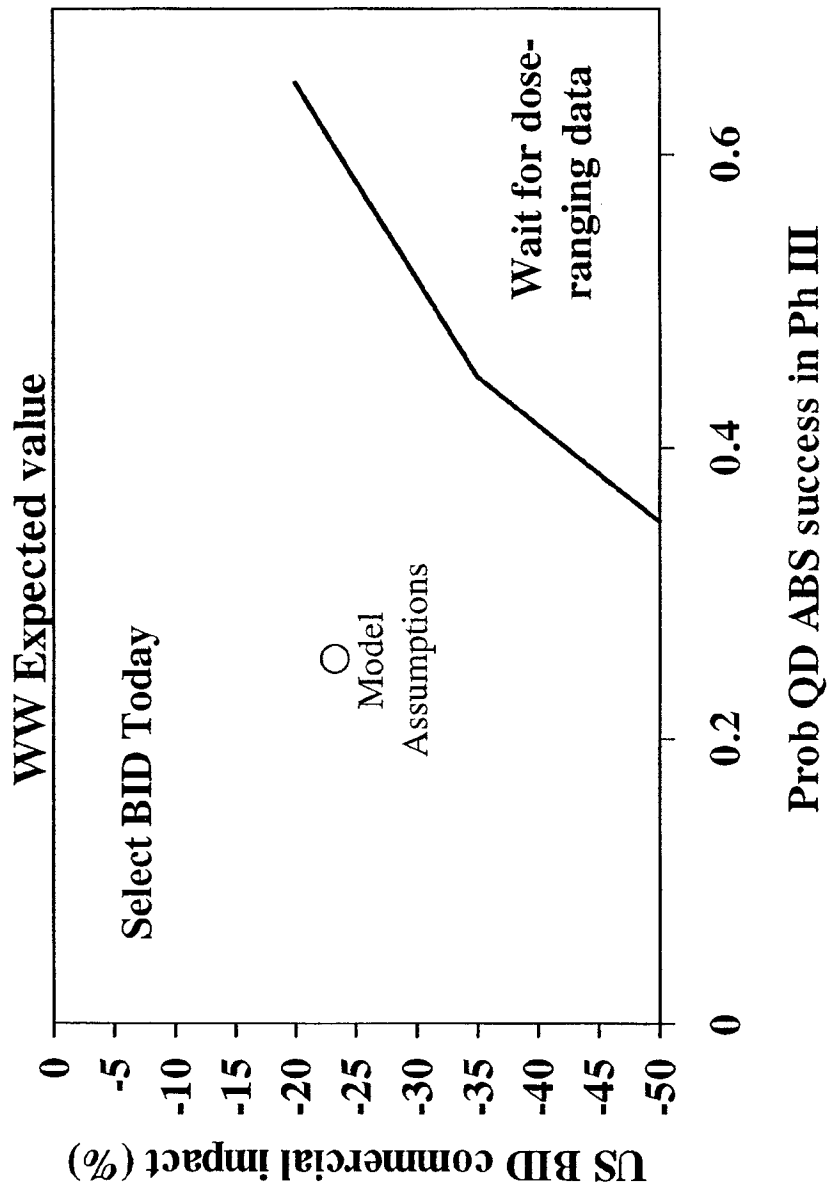
Six strategic alternatives were evaluated by the team on the basis of technical, regulatory and commercial attributes.

| Strategic Alternative | Description |
|-----------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Use ABS & CAP dose-ranging data | <ul style="list-style-type: none"> • Complete current ABS & CAP dose-ranging trials and then make dose decision. • Complete Phase III pivotal with selected dose. --Allows potential for split dosing for ABS & CAP in the US. |
| Use ABS dose-ranging data only | <ul style="list-style-type: none"> • Complete only the ABS dose-ranging study and then make a dose decision for both ABS & CAP. --If QD dose selected, obtain regulatory approval for conducting QD CAP pivotal. --If BID dose selected, proceed with BID dose for both ABS & CAP. |
| Select BID today | <ul style="list-style-type: none"> • Select the BID dose today for ABS & CAP Ph III pivotal. • Do not wait for completion of the dose-ranging studies. • Pursue a post-approval QD line-extension for the US & EU. |
| Select QD Today | <ul style="list-style-type: none"> • Select the QD dose today for ABS & CAP Ph III pivotal. • Do not wait for completion of the dose-ranging studies. |
| QD in the US & BID in the EU | <ul style="list-style-type: none"> • Develop BID in CAP & ABS for EU; Develop QD for US. • Do not wait for completion of the dose-ranging studies. |
| Phase III 3-arm CAP & ABS pivotal | <ul style="list-style-type: none"> • Expand the Phase III CAP program to allow for 3 arms per study – QD vs.. BID vs... comparator. • Drop one arm and continue with selected dose only (vs. comparator). |

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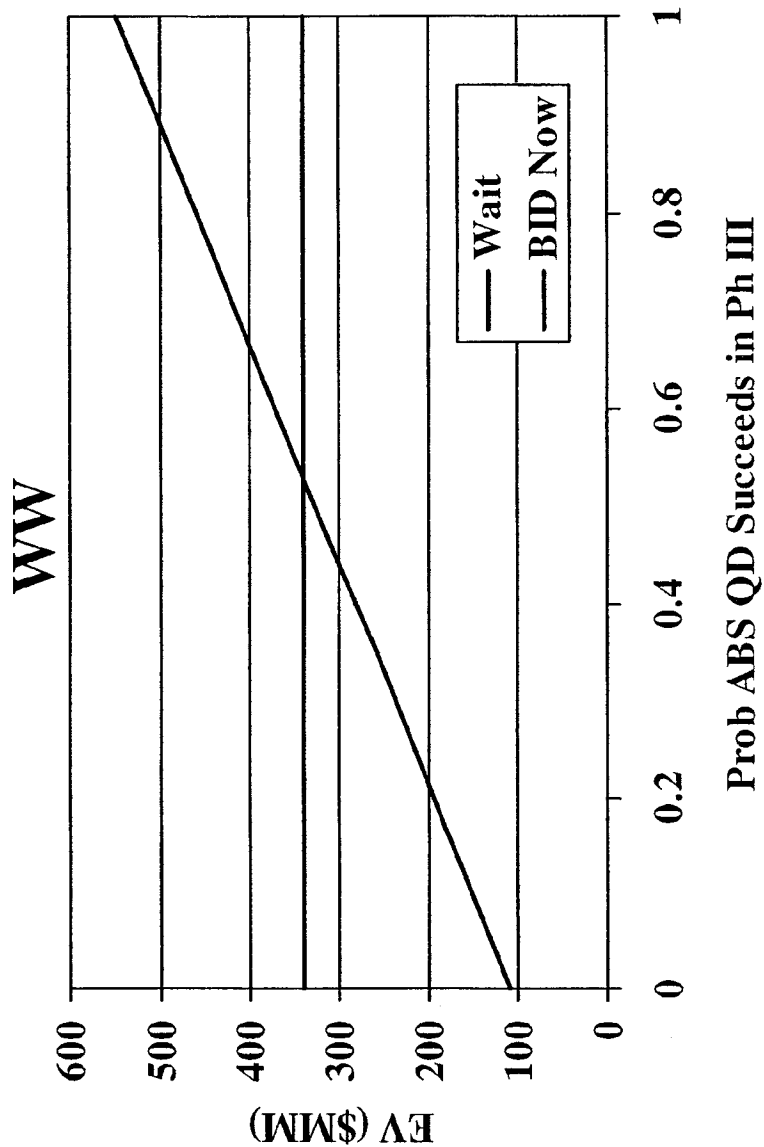
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Dual sensitivity to BID impact and ABS QD risk



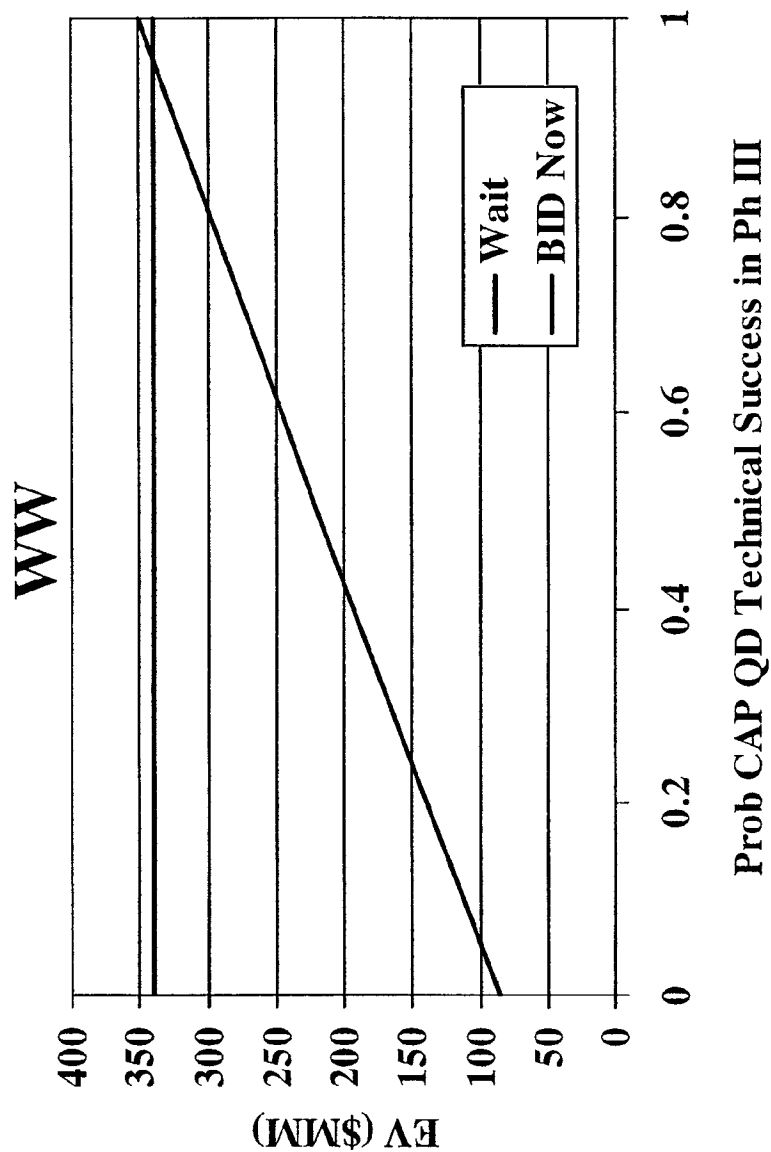
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Sensitivity to ABS QD prob in Ph III



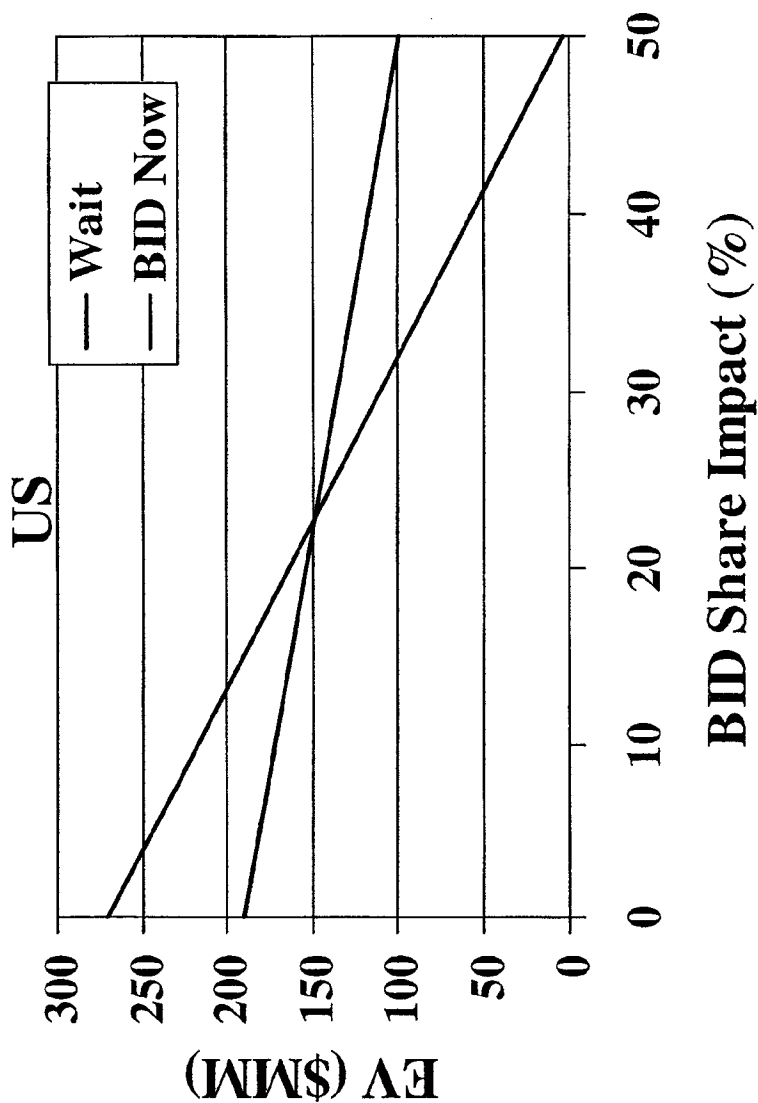
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Sensitivity to CAP QD risk in Ph III



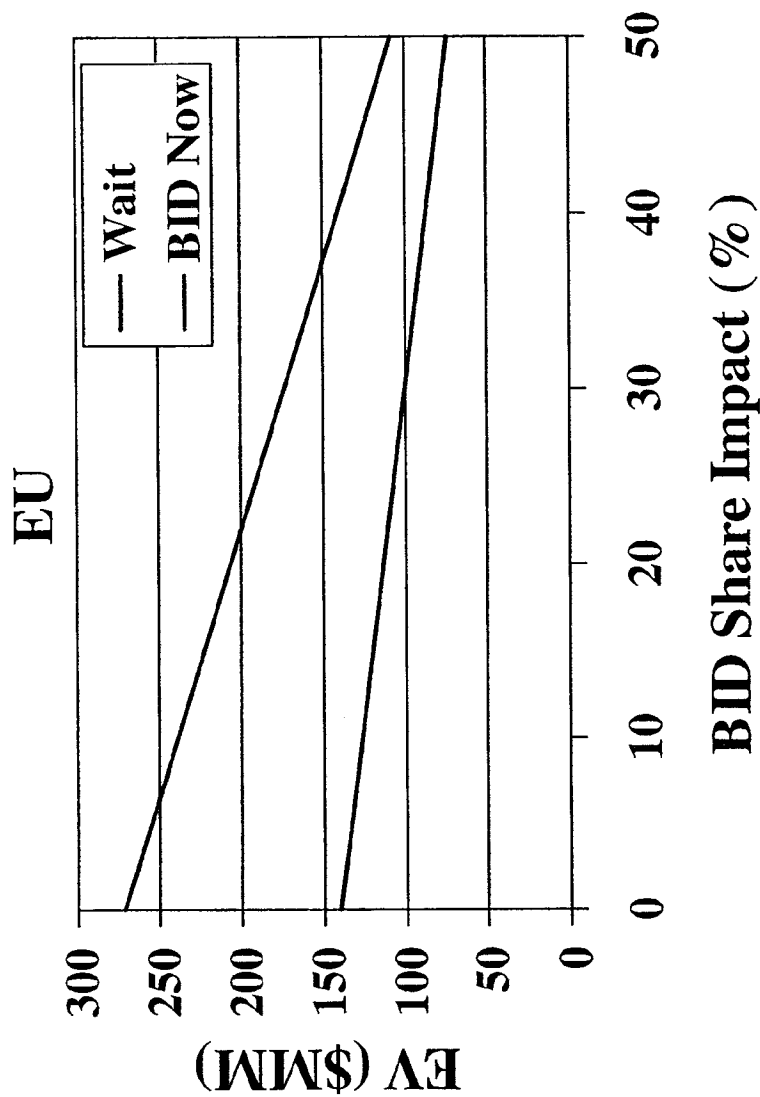
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Sensitivity to share impact



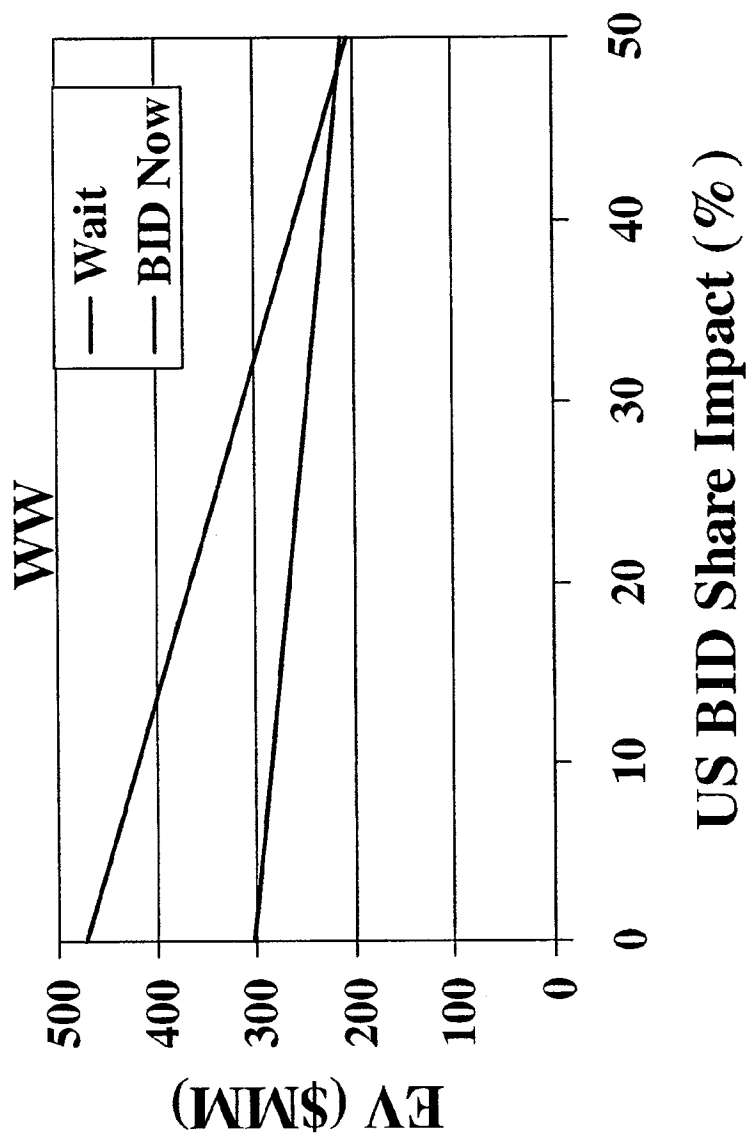
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Sensitivity to share impact



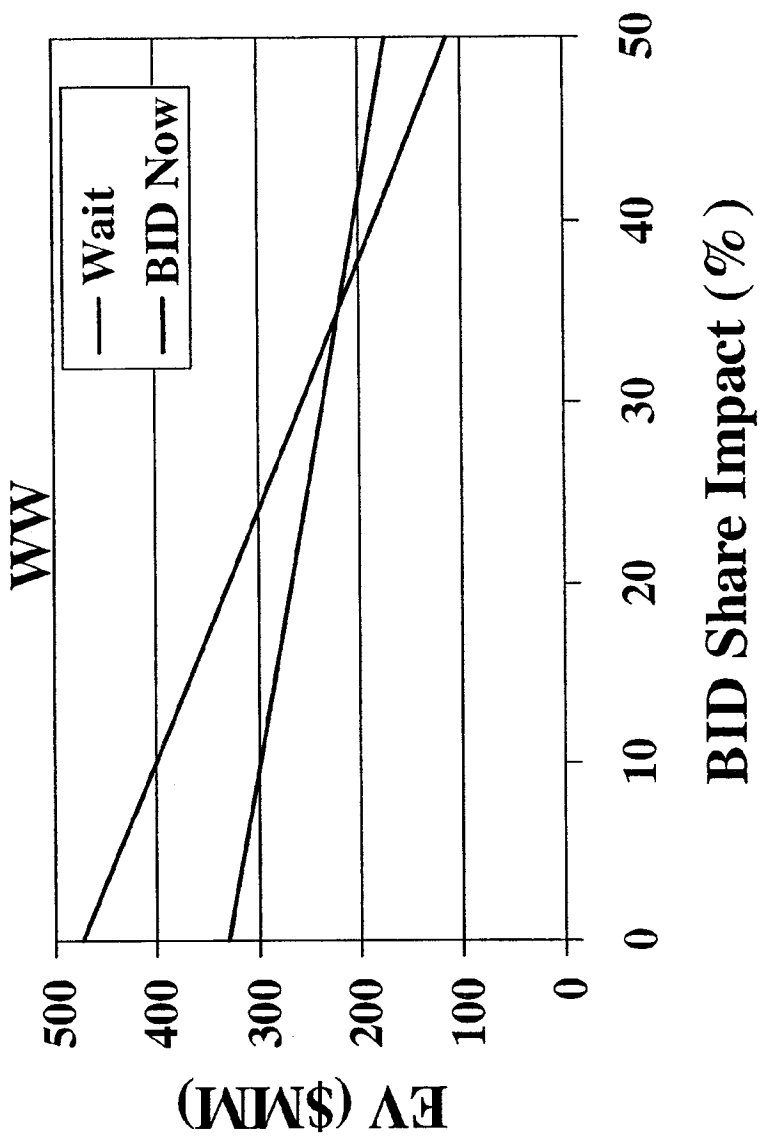
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Sensitivity of WW value to US share impact



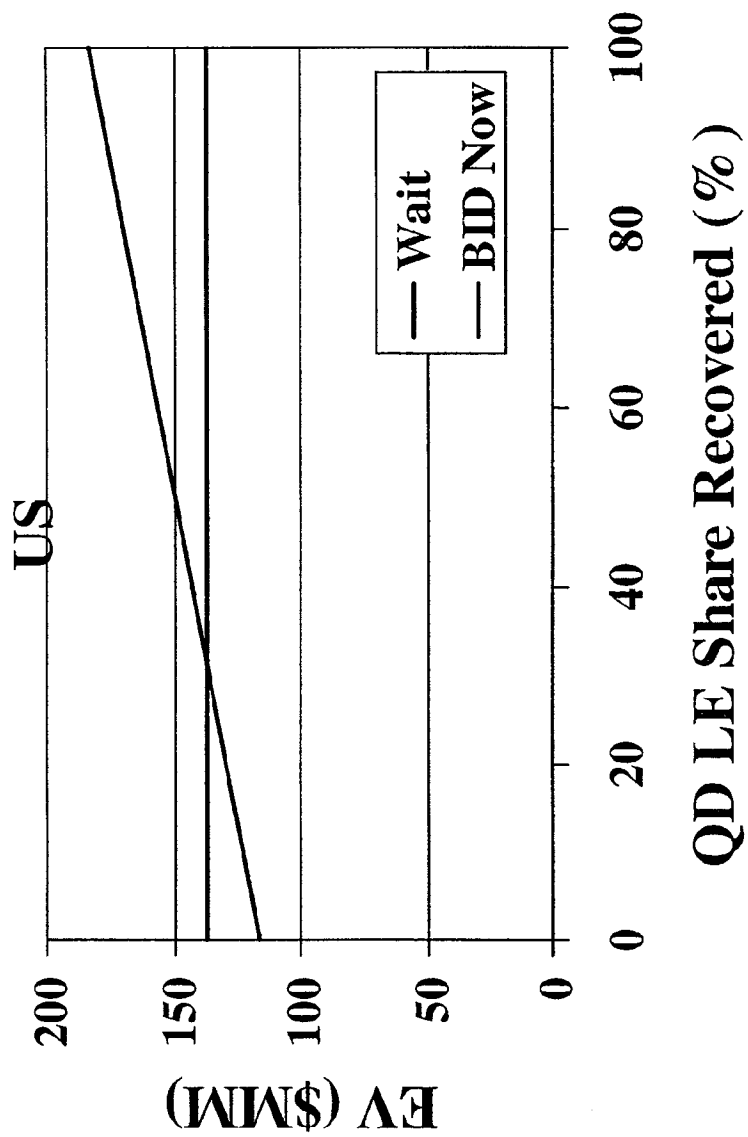
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Sensitivity to share impact



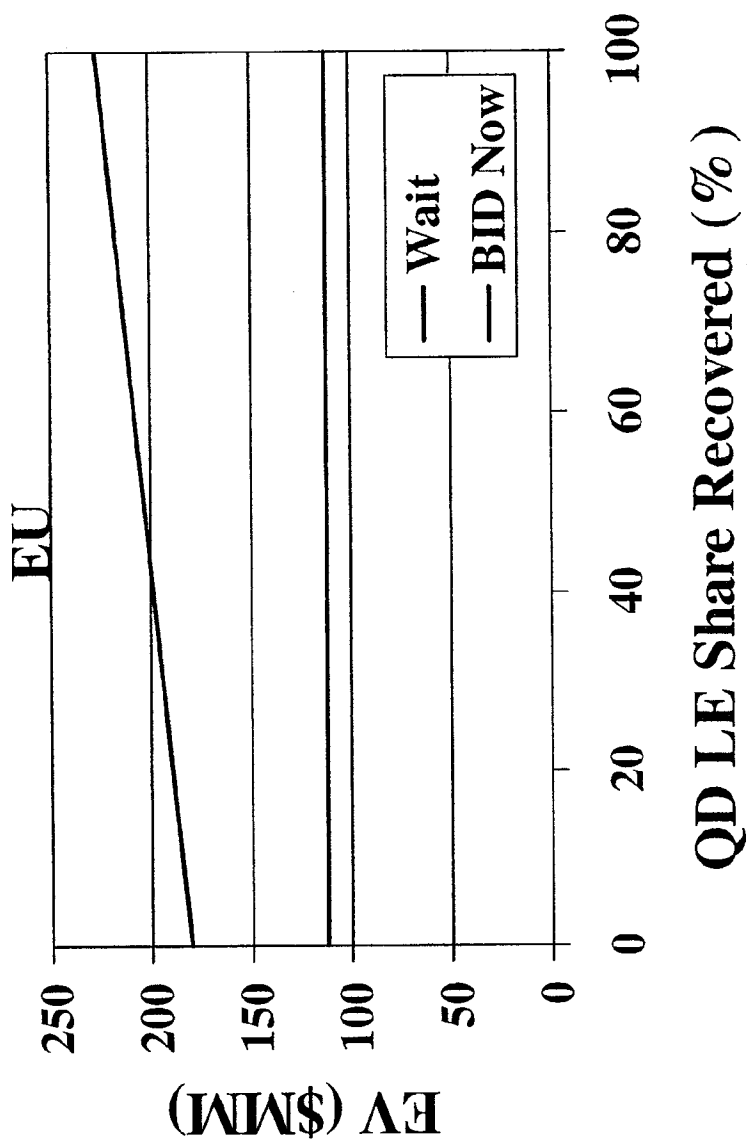
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Sensitivity to QD LE



07/23/2001

Sensitivity to QD LE



07/23/2001

| ABT-773 Ketolide Antibiotic - Tablet | | | | | | | | | | Indication(s) | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | |
|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----------------------------------------------------------------------|--------------------------|-------------------------|-------------|--------|-------------------------------------------------------------------------------------------------------------------|--------|--------|-------|---------------|-------|-------------------------------------------------|------------------------------------------------|---------------------|---------------------------------------------------------------------|-------------------------------------------|--------|--------------------------------------------------|-----------|------------------------|--------------------------------------------------------------|--------------------------------------------------------------------------------------------------------------------------|--------|--------------------------------------------------------------|------------------------|-------|-------------------------------------------------------------------|-----------------------------------------------------------------------|--------|---------|--------|--------|--------|--------|--------|-------|-------|-------|-------|-------|---------|-----|----|--------|--------|--------|--------|-------|--------|--------|-------|-------|-------|-------|-------|---------|-------------|----|-------|-------|-------|-------|--------|-------|-------|-------|-------|-------|-------|-------|--------|-------|----|--------|-------|-------|-------|--------|-------|-------|-------|-------|-------|-------|-------|--------|-------|---------|---------|--------|--------|--------|--------|--------|--------|-------|-------|-------|-------|-------|---------|
| Franchise | Dev. Status | Brand Name | Generic Name | Patent Exp. | 2017 | Branchitis, community-acquired pneumonia, sinusitis (QD pharyngitis trial being stopped due to efficacy concerns) | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Anti-Infective | Phase II | Afinal/Actegia (pending) | celastromycin (pending) | 2017 | 2017 | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | |
| <ul style="list-style-type: none">ABT-773 is a potent antibiotic that has excellent activity against respiratory pathogens, including penicillin/macrolide resistant <i>S. pneumoniae</i>.ABT-773 will be dosed 150 mg QD x 5 days for ABECB and pharyngitis; dosing for CAP and sinusitis will likely be 150 mg BID x 10 days. Phase IV studies to pursue QD dosing are being planned.ABT-773 will compete with macrolides on the basis of superior activity against resistant organisms (resistance claim being pursued) and improved mechanism and against quinolones on the basis of appropriate use and safety.BID dosing for CAP and sinusitis will present commercial challenges.Forecasts will be revised in November based on new clinical data on QD pharyngitis efficacy issues and LFT safety concerns. | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Key Competitors/Position to Market | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Key competitors are other macrolides (Zithromax), quinolones (Levaquin, Tequin, Avelex), Augmentin and cephalosporins (numerous). Avenitis ketolide Katak expected to re-file with additional data necessary for FDA marketing approval 3Q02. | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Augmentin and cephalosporins dominate most AI markets; quinolones dominate in Japan, with cepts a close second. New quinolones (leva, moxi gati) recently launched ex-Japan; however, current use is predominantly in more severe infections (e.g. CAP) due to safety concerns and premium pricing vs. other agents. Avenitis ketolide (Katak) expected to launch 4Q01 with inferior tolerability profile vs. ABT-773. | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Development Timeline | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | |
| <table><tr><th>Cost to NDA</th><th>DDC Est.</th><th>Thru 2000</th><th>YTD</th><th>Proj.</th><th>Budget</th><th>Var</th><th>2001</th><th>2002</th><th>2003</th><th>2004</th><th>2005</th><th>2006</th><th>Post LRP</th><th>Total</th></tr><tr><td>Clinicals</td><td>NA</td><td>\$35.9</td><td>\$48.5</td><td>\$63.9</td><td>\$62.2</td><td>-\$1.7</td><td>\$46.4</td><td>\$26.0</td><td>\$0.0</td><td>\$0.0</td><td>\$0.0</td><td>\$0.0</td><td>\$0.0</td><td>\$172.2</td></tr><tr><td>CMC</td><td>NA</td><td>\$77.3</td><td>\$11.2</td><td>\$18.9</td><td>\$20.5</td><td>\$1.6</td><td>\$16.3</td><td>\$10.6</td><td>\$0.0</td><td>\$0.0</td><td>\$0.0</td><td>\$0.0</td><td>\$0.0</td><td>\$123.1</td></tr><tr><td>Drug Safety</td><td>NA</td><td>\$8.8</td><td>\$1.5</td><td>\$2.0</td><td>\$1.9</td><td>-\$0.1</td><td>\$2.3</td><td>\$2.5</td><td>\$0.0</td><td>\$0.0</td><td>\$0.0</td><td>\$0.0</td><td>\$0.0</td><td>\$15.6</td></tr><tr><td>Other</td><td>NA</td><td>\$31.3</td><td>\$4.0</td><td>\$4.6</td><td>\$3.9</td><td>-\$0.7</td><td>\$5.1</td><td>\$5.1</td><td>\$0.0</td><td>\$0.0</td><td>\$0.0</td><td>\$0.0</td><td>\$0.0</td><td>\$46.1</td></tr><tr><td>TOTAL</td><td>\$200.0</td><td>\$153.3</td><td>\$65.4</td><td>\$69.4</td><td>\$68.5</td><td>-\$0.9</td><td>\$70.1</td><td>\$44.2</td><td>\$0.0</td><td>\$0.0</td><td>\$0.0</td><td>\$0.0</td><td>\$0.0</td><td>\$357.0</td></tr></table> | | | | | | | | | | | | Cost to NDA | DDC Est. | Thru 2000 | YTD | Proj. | Budget | Var | 2001 | 2002 | 2003 | 2004 | 2005 | 2006 | Post LRP | Total | Clinicals | NA | \$35.9 | \$48.5 | \$63.9 | \$62.2 | -\$1.7 | \$46.4 | \$26.0 | \$0.0 | \$0.0 | \$0.0 | \$0.0 | \$0.0 | \$172.2 | CMC | NA | \$77.3 | \$11.2 | \$18.9 | \$20.5 | \$1.6 | \$16.3 | \$10.6 | \$0.0 | \$0.0 | \$0.0 | \$0.0 | \$0.0 | \$123.1 | Drug Safety | NA | \$8.8 | \$1.5 | \$2.0 | \$1.9 | -\$0.1 | \$2.3 | \$2.5 | \$0.0 | \$0.0 | \$0.0 | \$0.0 | \$0.0 | \$15.6 | Other | NA | \$31.3 | \$4.0 | \$4.6 | \$3.9 | -\$0.7 | \$5.1 | \$5.1 | \$0.0 | \$0.0 | \$0.0 | \$0.0 | \$0.0 | \$46.1 | TOTAL | \$200.0 | \$153.3 | \$65.4 | \$69.4 | \$68.5 | -\$0.9 | \$70.1 | \$44.2 | \$0.0 | \$0.0 | \$0.0 | \$0.0 | \$0.0 | \$357.0 |
| Cost to NDA | DDC Est. | Thru 2000 | YTD | Proj. | Budget | Var | 2001 | 2002 | 2003 | 2004 | 2005 | 2006 | Post LRP | Total | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Clinicals | NA | \$35.9 | \$48.5 | \$63.9 | \$62.2 | -\$1.7 | \$46.4 | \$26.0 | \$0.0 | \$0.0 | \$0.0 | \$0.0 | \$0.0 | \$172.2 | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | |
| CMC | NA | \$77.3 | \$11.2 | \$18.9 | \$20.5 | \$1.6 | \$16.3 | \$10.6 | \$0.0 | \$0.0 | \$0.0 | \$0.0 | \$0.0 | \$123.1 | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Drug Safety | NA | \$8.8 | \$1.5 | \$2.0 | \$1.9 | -\$0.1 | \$2.3 | \$2.5 | \$0.0 | \$0.0 | \$0.0 | \$0.0 | \$0.0 | \$15.6 | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Other | NA | \$31.3 | \$4.0 | \$4.6 | \$3.9 | -\$0.7 | \$5.1 | \$5.1 | \$0.0 | \$0.0 | \$0.0 | \$0.0 | \$0.0 | \$46.1 | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | |
| TOTAL | \$200.0 | \$153.3 | \$65.4 | \$69.4 | \$68.5 | -\$0.9 | \$70.1 | \$44.2 | \$0.0 | \$0.0 | \$0.0 | \$0.0 | \$0.0 | \$357.0 | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Base Case Assumptions | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | |
| <table><tr><th>Product Profile (Efficacy, Safety, Convenience)</th><th>Base Case Assumptions</th><th>Share Impact</th></tr><tr><td>Efficacy: Comparable cure/eradication rates (75-90%) vs comparators</td><td>Resistance claim being targeted at launch</td><td>High</td></tr><tr><td>Efficacy: Adverse events comparable to Biaxin XL</td><td>Taste: 5%</td><td>Medium</td></tr><tr><td>Safety/AE: No major safety issues/product-specific labelling</td><td>Nausea: 5%</td><td>Medium</td></tr><tr><td>Safety/AE: 150 mg QD x 5 days dosing for ABECB & pharyngitis</td><td>Diarrhea: 5-10%</td><td>High</td></tr><tr><td>Conven: 150 mg BID x 10 days dosing for CAP & sinusitis at launch</td><td></td><td>High</td></tr><tr><td>Conven:</td><td></td><td>High</td></tr></table> | | | | | | | | | | | | Product Profile (Efficacy, Safety, Convenience) | Base Case Assumptions | Share Impact | Efficacy: Comparable cure/eradication rates (75-90%) vs comparators | Resistance claim being targeted at launch | High | Efficacy: Adverse events comparable to Biaxin XL | Taste: 5% | Medium | Safety/AE: No major safety issues/product-specific labelling | Nausea: 5% | Medium | Safety/AE: 150 mg QD x 5 days dosing for ABECB & pharyngitis | Diarrhea: 5-10% | High | Conven: 150 mg BID x 10 days dosing for CAP & sinusitis at launch | | High | Conven: | | High | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Product Profile (Efficacy, Safety, Convenience) | Base Case Assumptions | Share Impact | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Efficacy: Comparable cure/eradication rates (75-90%) vs comparators | Resistance claim being targeted at launch | High | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Efficacy: Adverse events comparable to Biaxin XL | Taste: 5% | Medium | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Safety/AE: No major safety issues/product-specific labelling | Nausea: 5% | Medium | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Safety/AE: 150 mg QD x 5 days dosing for ABECB & pharyngitis | Diarrhea: 5-10% | High | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | |
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| Conven: | | High | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Commercial Profile | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | |
| <table><tr><th>Launch Date</th><th>Price per Day at Launch (AWP)</th><th>Comparable to Z-Pak</th></tr><tr><td>Jan-05</td><td>\$8.78</td><td></td></tr><tr><td>Sales force @ peak sales (\$MM)</td><td>\$62</td><td></td></tr><tr><td>Promo @ peak sales (\$MM)</td><td>\$47</td><td></td></tr><tr><td>COGS @ launch, @ peak</td><td>\$3,000/kg, \$1,500/kg</td><td></td></tr><tr><td>Market/External/Other</td><td>Katak launches in 2003, additional quinolone entrant, market TRX flat</td><td></td></tr></table> | | | | | | | | | | | | Launch Date | Price per Day at Launch (AWP) | Comparable to Z-Pak | Jan-05 | \$8.78 | | Sales force @ peak sales (\$MM) | \$62 | | Promo @ peak sales (\$MM) | \$47 | | COGS @ launch, @ peak | \$3,000/kg, \$1,500/kg | | Market/External/Other | Katak launches in 2003, additional quinolone entrant, market TRX flat | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Launch Date | Price per Day at Launch (AWP) | Comparable to Z-Pak | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Jan-05 | \$8.78 | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Sales force @ peak sales (\$MM) | \$62 | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Promo @ peak sales (\$MM) | \$47 | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | |
| COGS @ launch, @ peak | \$3,000/kg, \$1,500/kg | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Market/External/Other | Katak launches in 2003, additional quinolone entrant, market TRX flat | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Ex-U.S. | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | |
| <table><tr><th>Mar-05</th><th>Equivalent to current clari 250 mg BID pricing</th></tr><tr><td>\$2.22</td><td></td></tr><tr><td>\$56</td><td></td></tr><tr><td>\$27</td><td></td></tr><tr><td>\$3,000/kg, \$1,500/kg</td><td></td></tr><tr><td>Quinolones used primarily in more severe RTI segment; Katak on market 4Q01 with inferior tolerability profile vs ABT-773</td><td></td></tr></table> | | | | | | | | | | | | Mar-05 | Equivalent to current clari 250 mg BID pricing | \$2.22 | | \$56 | | \$27 | | \$3,000/kg, \$1,500/kg | | Quinolones used primarily in more severe RTI segment; Katak on market 4Q01 with inferior tolerability profile vs ABT-773 | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | |
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| \$56 | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | |
| \$27 | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | |
| \$3,000/kg, \$1,500/kg | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | |
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| HIGHLY CONFIDENTIAL ABBT 0000726 | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Next Go/No Go Business Rationale | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Receipt of Phase III data 4Q01, dose selection for CAP & sinusitis | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | |
| ABT-773 represents a key product for the global anti-infective franchise given the patent expiration of clarithromycin 2004-2005. The product has a compelling selling proposition by virtue of its novel ketolide class and its activity against resistant organisms, provided it can deliver on safety, tolerability, and convenience dimensions. Katak regulatory issues in US may present opportunity. Likely BID dosing in some indications and relatively low PK profile represent potential issues | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | |

October 2001**ABT-773****Monthly Highlights – Key Project Progress**

- The Phase I QT Study, M01-325 was put on hold at the 2nd dosing period to allow for analysis of liver elevations seen in 4 subjects. Analysis is ongoing and a discussion with FDA is planned for the first week of November to discuss modifications to this study.
- The M00-219 CAP and M00-225 ABS QD vs BID studies were both ended in terms of enrolling patients as adequate numbers of subjects were enrolled for a dose decision as well as for the collection of pathogens. We will be planning an interim analysis of 400 CAP patients in mid December.
- The M00-223 Pharyngitis vs Penicillin V study final classification was completed in October. Blind breaking will take place in early November with study results available once final data queries are completed.
- Phase III CAP and ABS comparator study preparation is underway in the US and Europe. CRO training in the US was conducted Nov 1 and 2nd and is planned for Nov 15 and 16th in Europe. Enrollment is planned to initiate in mid-November.
- The initial Phase I study for the IV formulation will begin dosing November 22nd to evaluate dose levels, concentration and rates of infusion. A more detailed IV development plan will be finalized at the end of 2001 based on the initial Phase I results.
- The Japan program is continuing with the Phase I BAL study on track to initiate in November and the CAP Open Label study planned to initiate by the end of the year.
- Additional pediatric formulation development is being undertaken by PARD to optimize the initial formulations with a target of supplying clinical supplies for a Phase I study in adults by the end of 2nd quarter 2002. A pediatric development timeline is being developed to scope out activities to the filing with the key activity of initiating a Phase II study in children prior to the Tablet NDA.

Next Quarter's Key Progress Markers

| Key Progress Marker | Target Date |
|---------------------------------------------------------------------------------------------------------------------------------------------------|-------------|
| Complete final protocol and study preparation activities for the Phase III CAP and ABS pivotal studies (US and European) and initiate enrollment. | 11/15 |
| Initiate Phase I Single Dose study of IV formulation. | 11/22 |
| Complete interim analysis of M00-219 CAP QD vs BID study at 400 subjects. | 12/18 |
| Complete classification and finalize study results of all subjects in M00-219 CAP and M00-225 ABS QD vs BID studies. | 2/28/02 |
| Initiate Japan Open Label and BAL Tissue studies. | 12/01 |
| Complete European Pharyngitis (M00-222) and both European and US ABECB (M00-216 & M00-217) study enrollment. | 12/31 |
| Complete M01-311 definitive bioequivalence study (300L intermediate scale vs 1200L commercial scale) | 11/30 |

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October 2001

ABT-773

Key Project Issues and Risks

| Risk or Issue | Potential or Known Impact Check all that apply and Describe Impact <input checked="" type="checkbox"/> Cost <input checked="" type="checkbox"/> Time <input checked="" type="checkbox"/> X Profile <input checked="" type="checkbox"/> Regulatory | Strategy / Progress | Area / Responsibility | Resolution Date Planned / Actual |
|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----------------------|-------------------------------------|
| 150 mg QD vs BID dose decision in CAP/sinusitis. | <input checked="" type="checkbox"/> Cost <input checked="" type="checkbox"/> Time <input checked="" type="checkbox"/> X Profile <input checked="" type="checkbox"/> Regulatory Current AI opinion is that QD may receive regulatory challenge for approval in CAP unless data is very compelling given PK profile of 150 mg QD; however, BID dosing would result in a negative commercial impact. | Dose decision of 150mg BID was recommended to senior management on July 25 th . ABS QD vs BID interim analysis of 466 patients completed the end of Sept. Plans are going forward to initiate BID comparator studies for CAP and ABS in November. | Venture/GNPP/ DSG | 7/2001/7/2001 |
| Regulatory uncertainties over how to deal with the ketolide/macrolide class regarding QT interval effects. | <input checked="" type="checkbox"/> Cost <input checked="" type="checkbox"/> Time <input checked="" type="checkbox"/> X Profile <input checked="" type="checkbox"/> Regulatory Additional studies could be required to show no effects on QT. Class labeling could negatively impact sales of the product. | The QT study was put on hold Oct. 24 th due to liver elevations seen in 4 subjects. Data analysis is ongoing and a conference call with FDA is planned Nov 7th to discuss study modifications needed. | Regulatory | 6/2002 |
| The pharmacokinetic profile of QD dose could receive regulatory challenge or be viewed as sub-optimal commercially, particularly with respect to <i>H. influenzae</i> . | <input checked="" type="checkbox"/> Cost <input checked="" type="checkbox"/> Time <input checked="" type="checkbox"/> X Profile <input checked="" type="checkbox"/> Regulatory Support by PK/PPD experts is important for positioning this product in the marketplace. Competitors may challenge ABT 773 efficacy without expert support for the efficacy model. | Internal efforts to characterize ribosome binding properties are ongoing by Discovery, with an advisory will be planned with external experts to define further study. BAL tissue studies with 150mg QD and BID are ongoing. | Venture/GNPP | 07/2002 |
| Obtain sufficient quantity of clinical isolates with resistant organisms to request a separate claim for activity against resistant <i>S. pneumoniae</i> . | <input checked="" type="checkbox"/> Cost <input checked="" type="checkbox"/> Time <input checked="" type="checkbox"/> X Profile <input checked="" type="checkbox"/> Regulatory Without a sufficient number of isolates, we will not obtain a claim based on clinical results for activity against resistant pathogens. Will need to rely on in vitro data only to support this claim. | FDA feedback regarding a resistance claim for PRSP is that a sufficient "body of evidence" needs to be gathered to convince them to grant a claim. The Ketek FDA experience indicates that number of isolates, clinical success, and patient severity all figure into their decision. Based on DSG analysis, we have increased our CAP studies to target 25 resistant isolates to support the resistance claim. | Venture | 06/2002 |
| Phase I was repeated in Japan to further evaluate dose-ranging. A Japanese dose and formulation, as well as the Phase II/III studies, will be defined once the dose-ranging has been completed. This plan will determine the filing date for Japan. | <input checked="" type="checkbox"/> Cost <input checked="" type="checkbox"/> Time <input checked="" type="checkbox"/> X Profile <input checked="" type="checkbox"/> Regulatory | The Japan Phase I Dose-Ranging study results showed no difference between Japanese and Caucasians subjects and did not show liver elevations as seen in the Hawaii study. Japan will proceed with a Phase II Open Label (QD vs BID) study and Phase I BAL Tissue (BID) study by the end of 2001. | Japan | 08/2001/06/2001 |

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October 2001**ABT-773****Key Project Issues and Risks**

| Risk or Issue | Potential or Known Impact Check all that apply and Describe Impact <input checked="" type="checkbox"/> Cost <input type="checkbox"/> Time <input type="checkbox"/> Profile <input type="checkbox"/> Regulatory Phase I will proceed to a Go/No Go decision based on initial milestone funding. | Strategy / Progress | Area / Responsibility | Resolution Date Planned / Actual |
|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|------------------------------|--------------------------------------------|
| The initial development of an IV formulation has been completed and clinical supplies have been manufactured by HPD. Full development of the IV formulation has not been committed. | | The single-rising dose Phase I study protocol has been amended to incorporate changes to doses, concentrations used and infusion times to allow for additional evaluation of QT effects within this study. The study is planned to start in November. A Go/No go decision on the IV formulation can be made once results are available (Jan 2002). | HPD, Venture | 09/2001 |
| In light of the Ketec advisory focus on hepatic toxicity an a similar analysis of liver function tests has been undertaken for ABT 773 | <input type="checkbox"/> Cost <input type="checkbox"/> Time <input type="checkbox"/> Profile <input checked="" type="checkbox"/> Regulatory | A benchmark comparison to Clarithromycin as well as Ketek data is being undertaken. Visit to Univ of Texas opinion leader undertaken. Current data in his opinion will not adversely affect approvability. Ongoing safety reviews of LFT data planned at appropriate intervals. | Venture | 05/31 |

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October 2001**ABT-773****Key Activities**

| Commercial | | |
|----------------------------------------------------------|------|---------------------------------------------------------------------------------------------------------------|
| Activity | LBE | Actual |
| Completion of study tracking intranet | 3Q01 | Launched Sept 01 |
| Integration of intranet into communication plan | 4Q01 | |
| Integration of intranet into draft product label | 1Q02 | |
| Identification of communication vendor | 4Q01 | |
| Submission of brand/USAN names | 2Q01 | Ceftriaxone or velofamycin pending approval by WHO; Afina & Actega to be submitted to FDA 7/01 |
| Preliminary qualitative positioning research | 2Q02 | |
| Quantitative market research to support revised forecast | 3Q02 | |

| Formulation | | |
|------------------------------------------|---------|---------|
| Activity | Plan | Actual |
| Phase I Formulation (Caps)* | 12/1997 | 12/1997 |
| Phase II Formulation (Tablet) | 7/1999 | 8/1999 |
| Clinical Supplies Phase IIB | 7/1999 | 8/1999 |
| Phase III Formulation (Tablet) | 4/2000 | 7/2000 |
| Phase III Clinical Supplies Manufactured | 9/2000 | 9/2000 |
| NDA Lots (3) Completed | 7/2000 | 01/2001 |
| Completion of 1 Year Stability for NDA | 8/2001 | 8/2001 |
| Formulation Peer Review | 11/2002 | |

Plan Date:**Drug Substance****Actual Projected****Cost/kg****Actual****Plan****KG****Activity**

See the Following page for a
summary of Bulk Drug
deliveries in SPD.

Toxicology**Plan Date: 12/98**

| Toxicology Activity | Plan Start Date?? | Actual Start Date | Report Completed |
|------------------------------|----------------------|----------------------|---------------------|
| | 7/1997 | 6/1997 | 9/1998 |
| 2-week oral Rat/Monkey | 7/1997 | 6/1997 | 9/1998 |
| Acute Studies | 8/1997 | 8/1997 | 12/1997 |
| Mouse Lymphoma/Micronucleus | 11/1997 | 11/1997 | 4/1998 |
| 1 Month Rat/Monkey | 12/1997 | 12/1997 | 12/1998 |
| Pregnant Rat/Rabbit RF | 1/1998 | 1/1998 | 11/1998 |
| SEG II Rat/Rabbit | 3/1998 | 3/1998 | 2/1999 |
| Guinea pig sensitization | 11/1998 | 11/1998 | 2/1999 |
| 3 Month oral Rat/Monkey | 9/1999 | 10/6/1999 | 8/2000 |
| Seg I/III Rat | 9/1999 | 10/8/1999 | 12/2001 |
| IV Irritation studies, set 1 | 7/1999 | 7/15/1999 | 8/1999 |
| IV Irritation studies, set 2 | 2/2000 | 2/2000 | 3/2000 |
| IV 2-week Rat/Monkey Studies | 6/2000 | 6/2000 | 01/2001 |
| Neonatal/Juvenile Rat | 10/1999 | 11/1999 | 7/2000 |

* Target cost of drug substance at launch is \$2,500/kg (Finished Product)

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October 2001

ABT-773

SPD ABT-773 Bulk Drug Deliveries Update

| | Target Date | Amount | Delivery Date | Amount | Lot # | Amount after milling |
|-----------------------|-------------|--------|---------------|----------|--------------|----------------------|
| Campaign 1 | 2/28/99 | 200 Kg | 2/23/99 | 209 Kg | 50-007-CA-00 | 207.5 Kg (2/26)* |
| Campaign 2a | 6/15/99 | 140 Kg | 6/17/99 | 131 Kg | 54-702-NI-00 | 129.4 Kg (6/19)* |
| Campaign 2b | 7/15/99 | 140 Kg | 7/21/99 | 121.5 Kg | 55-208-CB-00 | 119.3 Kg (8/4)* |
| Tox lot | 8/30/99 | 5 Kg | 8/25/99 | 6.1 Kg | 55-718-NI-00 | |
| Campaign 3a | 9/30/99 | 160 Kg | 10/8/99 | 170.5 Kg | 58493CB00 | 138.4 Kg (10/16)* |
| Campaign 3b | 10/21/99 | 160 Kg | 10/11/99 | 176.5 Kg | 58494CB00 | 169.5 Kg (10/16)* |
| Pilot run 1 | ----- | 15 Kg | 10/30/99 | 18.9 Kg | 59763N100 | no milling |
| Pilot run 2 | ----- | 15 Kg | 2/5/00 | 15.5 Kg | 61790NI00 | no milling |
| Pilot run 3 | ----- | 25 Kg | 1/30/00 | 27.5 Kg | 62764CB00 | 27.3 Kg (4/18)* |
| Campaign 4 | 12/10/99 | 320 Kg | 11/23/99 | 355 Kg | 61741CB00 | 309 Kg (3/2)* |
| Campaign 5 | 12/30/99 | 300 Kg | 12/16/99 | 300.5 Kg | 60665CB00 | 269.2 Kg (3/3)* |
| Campaign 6 | 2/28/00 | 280 Kg | 2/23/00 | 321 Kg | 62796CB00 | 315.5 Kg (3/6)* |
| Campaign 6 (IV) | 2/28/00 | 15 Kg | 2/22/00 | 20 Kg | 62797CB00 | 18 Kg (3/15)* |
| Campaign 7 | 3/30/00 | 300 Kg | 4/10/00 | 370 Kg | 63890CB00 | 361.2 Kg (4/18)* |
| Campaign 7 (IV) | 3/30/00 | 5 Kg | 3/29/00 | 19 Kg | 63889CB00 | 17.2 Kg (4/11)* |
| Campaign 8 | 4/25/00 | 200 Kg | 5/11/00 | 263 Kg | 64970CB00 | 256.5 Kg (5/15) |
| Campaign 8 (IV) | 4/25/00 | 15 Kg | 4/25/00 | 19.8 Kg | 64971CB00 | 17.7 Kg (5/11)* |
| Campaign 9 | 6/15/00 | 300 Kg | 6/14/00 | 375.7 Kg | 65064CB00 | 355.7 Kg (6/20/00) |
| Campaign 9 (IV) | 6/15/00 | 15 Kg | 6/5/00 | 18.1 Kg | 65065CB00 | 16.7 Kg (6/9/00)* |
| Campaign 10 | 7/15/00 | 300 Kg | 7/26/00 | 361.2 Kg | 67176CB00 | 359.0 Kg (8/10/00) |
| Campaign 11 | 8/15/00 | 300 Kg | 8/4/00 | 333.7 Kg | 68285CB00 | 271.9 Kg (9/7/00) |
| Campaign 12 | 10/6/00 | 300 Kg | 9/27/00 | 356 Kg | 69458CB00 | 292.3 Kg (12/8/00) |
| Campaign 13 | 11/23/00 | 300 Kg | 11/15/00 | 351.2 Kg | 71665CB00 | 349.1 Kg (12/20/00) |
| Total (year 2000) | | | | | | 2,815.5 Kg |
| Campaign 14 | 1/28/01 | 300 Kg | 1/26/01 | 327.5 Kg | 73886CB00 | 318.9 Kg (02/13/01) |
| Campaign 15 | 2/10/01 | 330 Kg | 1/14/01 | 354.9 Kg | 71699CB00 | 353.8 Kg (02/02/01) |
| * Weight after rework | | | | | | |

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October 2001

All Clinical Studies:

[illegible]

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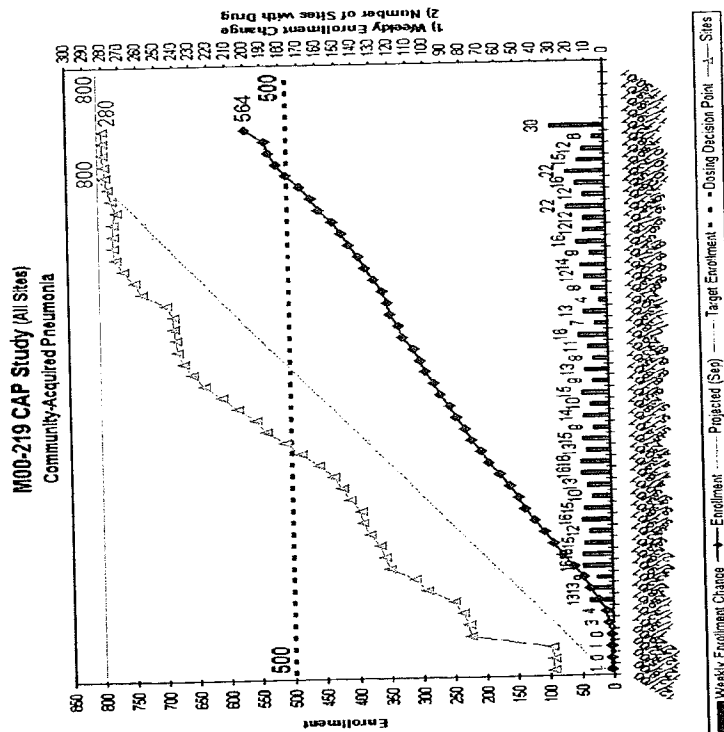
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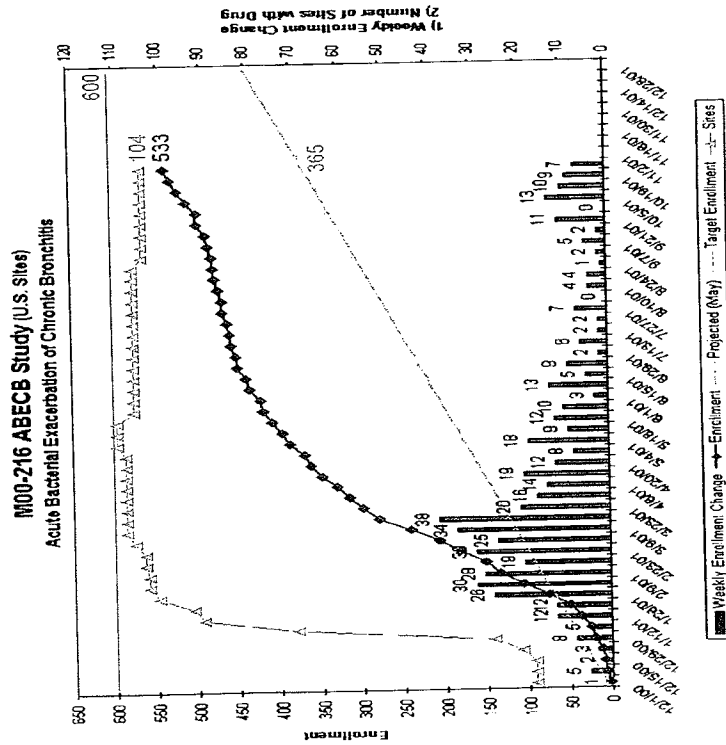
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October 2001**ABT-773****Ongoing Clinical Studies** (List first time in man, Phase II Dose-Ranging and Pivotal Trials)**M00-219 – Dose-Ranging CAP**

Protocol: Dose selection.
 Objective: 150mg QD vs 150mg BID, 10 days
 ABT-773 Doses: None
 Comparator Doses: 800
 Target Enrollment: Currently enrolling
 Status: Currently enrolling
 Major Findings:

**M00-216 – Phase III ABECB vs Azithromycin**

Safety & Efficacy
 150mg QD, 5 days
 Azithromycin 500mg day 1, 250mg QD for 4 days
 600
 Currently Enrolling



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Ongoing Clinical Studies (List first time in man, Phase II Dose-Ranging and Pivotal Trials)

M00-217 - Phase III ABECB vs Levofloxacin

Use Collection

150mg QD vs 150mg BID, 10 days

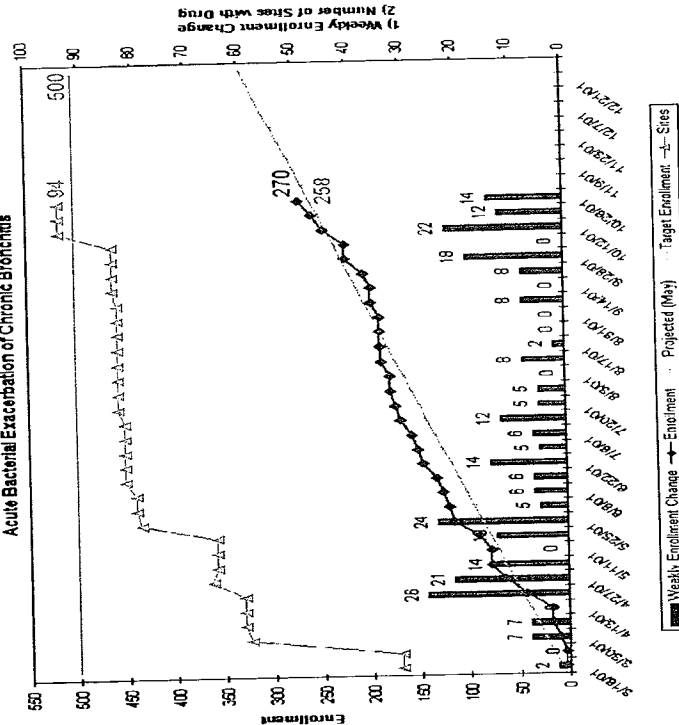
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Levofloxacin 500mg QD for 7 days

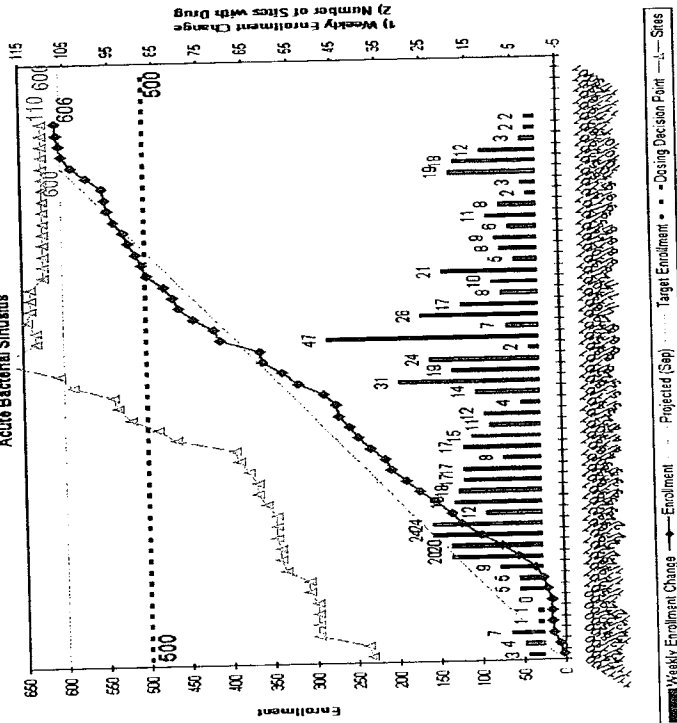
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Currently enrolling

M00-217 ABECB Study (Ex-U.S. Sites)
Acute Bacterial Exacerbation of Chronic Bronchitis



M00-225 ABS Study (All Sites)
Acute Bacterial Sinusitis



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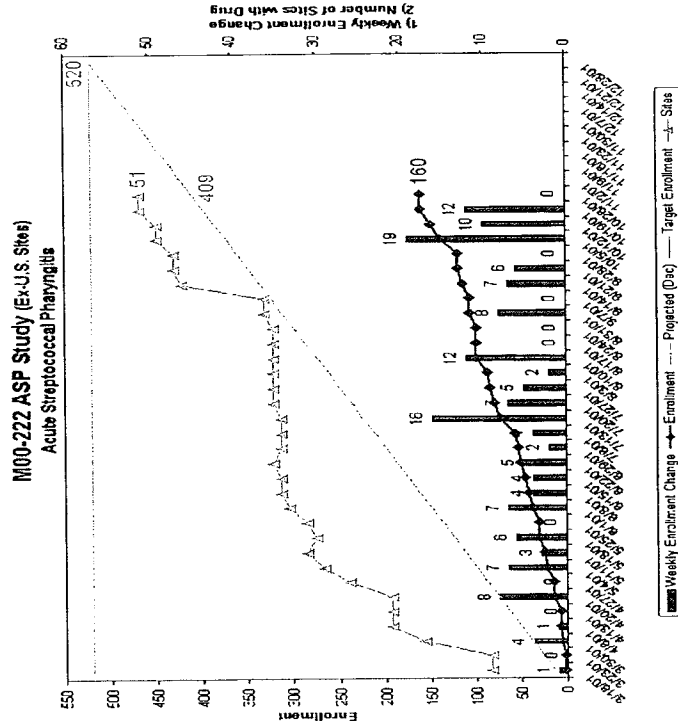
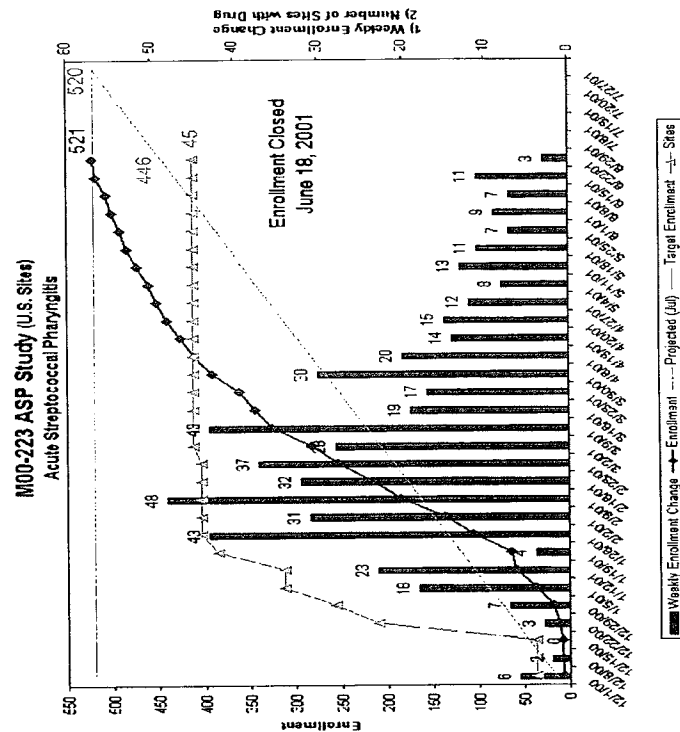
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ABT-773

October 2001

Ongoing Clinical Studies (List first time in man, Phase II Dose-Ranging and Pivotal Trials)

| | |
|--------------------|---------------------------------------------------------|
| Protocol: | M00-223 - Phase III Pharyngitis vs Penicillin 500mg TID |
| Objective: | Safety & Efficacy |
| ABT-773 Doses: | 150mg QD., 5days |
| Comparator Doses: | Penicillin 500 mg TID, 10 days |
| Target Enrollment: | 520 |
| Status: | Currently enrolling |
| Major Findings: | |

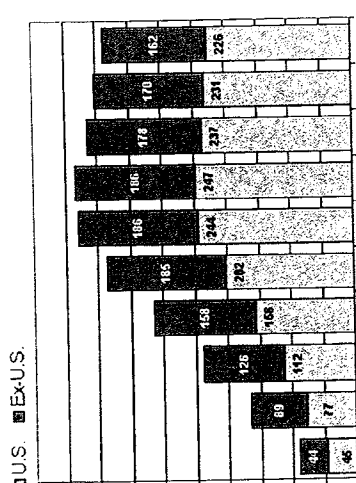


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| ABT-773 Ketolide Antibiotic - Tablet | | | | | | | | | | Indicator(s) | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | |
|---------------------------------------------------------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|------------|-------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|--------|--------|--------|--------|-------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-------|-------|-------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-------|-------|-------|-------|-----------------------------------------------------------------------|--------------------------------------------|-------|-------|-------|-------|-------|-------|-------|-------|--------------------------------------------------------------------|------------------------------------------------------|--|--|--|--|--|--|--|--|--|
| Franchise | Dev. Status | Brand Name | Generic Name | Patent Exp. | 2017 | | | | | Bronchitis, community-acquired pneumonia, sinusitis (150 mg QD prn/initials trial stopped due to efficacy) | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Description | Anti-infective | Phase III | Actemio (pending) | celtromycin | 2017 | | | | | Bronchitis, community-acquired pneumonia, sinusitis (150 mg QD prn/initials trial stopped due to efficacy) | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | |
| | ABT-773 is a potent antibiotic that has excellent activity against respiratory pathogens, including penicillin/macrolide resistant <i>S. pneumoniae</i> . | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | |
| | ABT-773 will be dosed 150 mg QD x 5 days for ABECB, dosing for CAP and sinusitis will be 150 mg BID x 10 days. | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | |
| | ABT-773 will compete with macrolides on the basis of superior activity against resistant organisms (resistance claim being pursued) and improved mechanism and against quinolones on the basis of appropriate use and safety | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | |
| BID dosing for CAP and sinusitis will present commercial challenges | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | |
| U.S. Market | Unit | Value | %96-00 | Unmet Need/Key Market Drivers | | | | | | | | | | | Key Competitors/Position to Market | | | | | | | | | | | | | | | | | | | | | | | | | |
| | TRX | 217 MM | 0.1% | Unmet need in community RTI is low. Key market drivers are tolerability, convenience, resistance (ability to treat resistant organisms along with low propensity to lose patent exclusivity in 2003-2005 (Biaxin, Zithromax, Levaquin, Cipro), which may negatively impact future prices. | | | | | | | | | | | Key competitors are other macrolides (Zithromax), quinolones (Leraquin, Tequin, Aveiox), Augmentin and cephalosporins (numerous). Aventis ketolide Ketek expected to re-file with additional data necessary for FDA marketing approval in late 2002. | | | | | | | | | | | | | | | | | | | | | | | | | |
| | Sales | \$6,081 MM | 9.5% | Need exists for agents active against pen and macrolide resistant pathogens, without the safety concerns currently associated with the quinolone class. Pharmacoeconomic issues are of increasing concern to government-controlled healthcare systems, leading to higher hurdles for regulatory approval regarding therapeutic benefit vs. existing therapies, since price/reimbursement controls, and push for shorter courses of therapy. | | | | | | | | | | | Augmentin and cephalosporins dominate most AI markets, quinolones dominate in Japan, with cephs a close second. New quinolones (Iavo, moxi gati) recently launched ex-Japan, however, current use is predominantly in more severe infections (e.g. CAP) due to safety concerns and premium pricing vs. other agents. Aventis ketolide (Ketek) launch 4Q01 in Germany. | | | | | | | | | | | | | | | | | | | | | | | | | |
| | TRX | 824 MM | 0.4% | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Ex-U.S. Market | Sales | \$6,644 MM | 5.9% | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | |
| | Cost to NDA | DDC Est. | Thru | 2002 | | 2003 | | 2004 | | 2005 | | 2006 | | 2007 | | 2008 | | 2009 | | 2010 | | 2011 | | 2012 | | 2013 | | 2014 | | 2015 | | | | | | | | | | |
| | Clinicals | NA | \$35.9 | \$4.9 | \$55.2 | \$55.2 | \$0.0 | \$51.2 | \$26.0 | \$0.0 | \$0.0 | \$0.0 | \$0.0 | \$0.0 | \$0.0 | \$0.0 | \$0.0 | \$0.0 | \$0.0 | \$0.0 | \$0.0 | \$0.0 | \$0.0 | \$0.0 | \$0.0 | \$0.0 | \$0.0 | \$0.0 | \$0.0 | \$0.0 | | | | | | | | | | |
| | CMC | NA | \$77.3 | \$1.0 | \$19.7 | \$19.7 | \$0.0 | \$19.7 | \$10.6 | \$0.0 | \$0.0 | \$0.0 | \$0.0 | \$0.0 | \$0.0 | \$0.0 | \$0.0 | \$0.0 | \$0.0 | \$0.0 | \$0.0 | \$0.0 | \$0.0 | \$0.0 | \$0.0 | \$0.0 | \$0.0 | \$0.0 | \$0.0 | \$0.0 | | | | | | | | | | |
| Development (to NDA, excludes Japan) | Drug Safety | NA | \$8.8 | \$0.3 | \$2.5 | \$2.5 | \$0.0 | \$2.5 | \$2.5 | \$0.0 | \$0.0 | \$0.0 | \$0.0 | \$0.0 | \$0.0 | \$0.0 | \$0.0 | \$0.0 | \$0.0 | \$0.0 | \$0.0 | \$0.0 | \$0.0 | \$0.0 | \$0.0 | \$0.0 | \$0.0 | \$0.0 | \$0.0 | \$0.0 | | | | | | | | | | |
| | Other | NA | \$31.3 | \$0.0 | \$2.3 | \$2.3 | \$0.0 | \$6.3 | \$5.1 | \$0.0 | \$0.0 | \$0.0 | \$0.0 | \$0.0 | \$0.0 | \$0.0 | \$0.0 | \$0.0 | \$0.0 | \$0.0 | \$0.0 | \$0.0 | \$0.0 | \$0.0 | \$0.0 | \$0.0 | \$0.0 | \$0.0 | \$0.0 | \$0.0 | | | | | | | | | | |
| | TOTAL | \$200.0 | \$153.3 | \$6.2 | \$79.7 | \$79.7 | \$0.0 | \$79.7 | \$44.2 | \$0.0 | \$0.0 | \$0.0 | \$0.0 | \$0.0 | \$0.0 | \$0.0 | \$0.0 | \$0.0 | \$0.0 | \$0.0 | \$0.0 | \$0.0 | \$0.0 | \$0.0 | \$0.0 | \$0.0 | \$0.0 | \$0.0 | \$0.0 | \$0.0 | | | | | | | | | | |
| | Actual | Jun-97 | Dec-97 | Oct-97 | Dec-98 | Sep-99 | Jun-00 | Jun-03 | Aug-03/Aug-03/TBD | Aug-04/Jun-05/TBD | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Commercial (excludes Japan) | Base Case Forecast | | | | | | | | | | Product Profile (Efficacy, Safety, Convenience) | | | | | | | | | | Base Case Assumptions | | | | | | | | | | Share Impact | | | | | | | | | |
| | U.S. Ex-U.S. | | | | | | | | | | Efficacy: Comparable cure/radiation rates (75-90%) vs comparators Efficacy: Resistance claim being targeted at launch Safety/AE: Adverse events comparable to Biaxin XL Safety/AE: No major safety issues/product-specific labelling Conven: 150 mg QD x 5 days dosing for ABECB Conven: 150 mg BID x 10 days dosing for CAP & sinusitis at launch | | | | | | | | | | Taste: 5% Nausea: 5% Diarrhea: 5-10% | | | | | | | | | | Medium Medium Medium Medium High High | | | | | | | | | |
| |  | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | |
| | Financial Summary | | | | | | | | | | Commercial Profile | | | | | | | | | | U.S. | | | | | | | | | | Ex-U.S. | | | | | | | | | |
| Peak Sales (\$MM) | | | | | | | | | | Launch Date | | | | | | | | | | Jan-06 | | | | | | | | | | estimate | | | | | | | | | | |
| Peak Standard Margin (\$MM) | | | | | | | | | | Price per Day at Launch (AWP) | | | | | | | | | | \$6.78 | | | | | | | | | | Equivalent to current clari 250 mg BID pricing | | | | | | | | | | |
| Peak Standard Margin (%) | | | | | | | | | | Sales force @ peak sales (\$MM) | | | | | | | | | | \$62 | | | | | | | | | | \$56 | | | | | | | | | | |
| | | | | | | | | | | Promo @ peak sales (\$MM) | | | | | | | | | | \$47 | | | | | | | | | | \$27 | | | | | | | | | | |
| | | | | | | | | | | COGS @ launch, @ peak | | | | | | | | | | \$3,000/kg, \$1,500/kg | | | | | | | | | | \$3,000/kg, \$1,500/kg | | | | | | | | | | |
| | | | | | | | | | | Market/External/Other | | | | | | | | | | Ketek launches in 2003, additional quinolone entrant, market TRX flat | | | | | | | | | | Ketek on market 4Q01 with inferior tolerability profile vs ABT-773 | | | | | | | | | | |
| Next Go/No Go Business Rationale | | | | | | | | | | Results of US ABECB M00-216 available in March 2002. Other Phase III trials are on-hold because the winter season is coming to a close. Reassessment of overall program expected in 3Q02 | | | | | | | | | | | | | | | | | | | | But loss | | | | | | | | | | |

March 2002**ABT-773****Monthly Highlights – Key Project Progress**

- The Phase I QT Study, M01-325 was re-started in March with 28 subjects returning to be screened. The subjects will be completed by the end of April and preliminary results are targeted for early June.
- The Phase III EU ASP study is the only study currently with ongoing enrollment. ASP enrollment is lagging behind with 378 patients (projected completion, 520 pts by the end of April).
- The Japan Phase II Open label study has enrolled 15 patients (target 40 pts) the planned completion date of May 2002 has been extended to Sept 2002 due to the poor respiratory season in Japan.
- The CAP QD vs BID study (M00-219) is undergoing data clean-up and classification currently and the plan is to have this completed by the end of April. Once final issues from classification have been resolved, preliminary results will be available.

Next Quarter's Key Progress Markers

| Key Progress Marker | Target Date |
|-----------------------------------------------------------|-------------|
| Preliminary results for M00-219 CAP QD vs BID study. | 05/15/02 |
| Complete European Pharyngitis (M00-222) enrollment. | 04/30/02 |
| Preliminary results for M00-216 ABECB US study. | 04/30/02 |
| Close the final database for M00-225 ABS and break blind. | 04/30/02 |
| Complete all subjects in the M01-325 study. | 04/30/02 |
| Complete Japan Open Label study. | 09/30/02 |

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March 2002**ABT-773****Key Project Issues and Risks**

| Risk or Issue | Potential or Known Impact Check all that apply and Describe Impact ___ Cost ___ Time ___ Profile ___ Regulatory Additional studies could be required to show no effects on QT. Class labeling could negatively impact sales of the product. | Strategy / Progress | Area / Responsibility | Resolution Date Planned / Actual |
|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|------------------------------|--------------------------------------------|
| Regulatory uncertainties over how to deal with the ketolide/macrolide class regarding QT interval effects. | ___ Cost ___ Time ___ Profile ___ Regulatory Additional studies could be required to show no effects on QT. Class labeling could negatively impact sales of the product. | The M01-325 QT study restarted March 8 th . | Regulatory | 6/2002 |
| The pharmacokinetic profile of QD dose could receive regulatory challenge or be viewed as sub-optimal commercially, particularly with respect to <i>H. influenzae</i> . | ___ Cost ___ Time ___ Profile ___ Regulatory Support by PK/PD experts is important for positioning this product in the marketplace. Competitors may challenge ABT 773 efficacy without expert support for the efficacy model. | Internal efforts to characterize ribosome binding properties are ongoing by Discovery, with an advisory will be planned with external experts to define further study. The 150mg QD and BID BAL study (Gottfried) and the Japan BAL study are both complete. Sample analysis is ongoing. One additional tissue study (Conte) is projected to complete in 1Q 2002. | Venture/GNPP | 07/2002 |
| Obtain sufficient quantity of clinical isolates with resistant organisms to request a separate claim for activity against resistant <i>S. pneumoniae</i> . | ___ Cost ___ Time ___ Profile ___ Regulatory Without a sufficient number of isolates, we will not obtain a claim based on clinical results for activity against resistant pathogens. Will need to rely on in vitro data only to support this claim. | FDA feedback regarding a resistance claim for PRSP is that a sufficient "body of evidence" needs to be gathered to convince them to grant a claim. The Ketek FDA experience indicates that number of isolates, clinical success, and patient severity all figure into their decision. Based on DSG analysis, we have increased our CAP studies to target 25 resistant isolates to support the resistance claim. | Venture | 06/2002 |
| Phase I was repeated in Japan to further evaluate dose-ranging. A Japanese dose and formulation, as well as the Phase II/III studies, will be defined once the dose-ranging has been completed. This plan will determine the filing date for Japan. | ___ Cost ___ Time ___ Profile ___ Regulatory Phase I will proceed to a Go/No Go decision based on initial milestone funding. | The Japan Phase II Open Label (QD vs BID) study has started enrolling with a projected completion in April 2002. Due to a poor respiratory season in Japan, enrollment on this study has been delayed. Taisho and Dainabot are currently projecting a Sept. 2002 completion date. | Japan | 08/2001/06/2001 |
| The initial development of an IV formulation has been completed and clinical supplies have been manufactured by HPD. Full development of the IV formulation has not been committed. | ___ Cost ___ Time ___ Profile ___ Regulatory Phase I will proceed to a Go/No Go decision based on initial milestone funding. | Based on the delay to the tablet Phase III program, the decision was made to discontinue development of the IV formulation at this time. | HPD, Venture | 09/2001 |

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March 2002**ABT-773****Key Project Issues and Risks**

| Risk or Issue | Potential or Known Impact Check all that apply and Describe Impact ___ Cost ___ Time ___ Profile <input checked="" type="checkbox"/> Regulatory | Strategy / Progress | Area / Responsibility | Resolution Date Planned / Actual |
|-----------------------------------------------------------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|------------------------------|--------------------------------------------|
| In light of the Ketec advisory focus on hepatic toxicity an a similar analysis of liver function tests has been undertaken for ABT 773. | | Ongoing safety reviews of LFT data planned at appropriate intervals. An amendment to add additional LFT monitoring during study treatment has been made to the Phase III CAP and ABS studies. Study enrollment will not start in the current winter respiratory season. | Venture | 03/02 |

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March 2002**ABT-773****Key Activities**

| Commercial | | LBE | | Actual |
|----------------------------------------------------------|--|---------|-------------------------------------------|--------|
| Activity | | | | |
| Completion of study tracking intranet | | 3Q01 | Launched Sept01 | |
| Integration of intranet into communication plan | | On hold | On hold | |
| Integration of intranet into draft product label | | On hold | On hold | |
| Identification of communication vendor | | On hold | On hold | |
| Submission of brand/USAN names | | 2Q01 | Cethromycin formally approved on 12/26/01 | |
| Preliminary qualitative positioning research | | On hold | On hold | |
| Quantitative market research to support revised forecast | | On hold | On hold | |

| Formulation | | Plan | | Plan Date: 12/98 |
|------------------------------------------|--|---------|--|------------------|
| Activity | | | | Actual |
| Phase I Formulation (Caps)* | | 12/1997 | | 12/1997 |
| Phase II Formulation (Tablet) | | 7/1999 | | 8/1999 |
| Clinical Supplies Phase IIB | | 7/1999 | | 8/1999 |
| Phase III Formulation (Tablet) | | 4/2000 | | 7/2000 |
| Phase III Clinical Supplies Manufactured | | 9/2000 | | 9/2000 |
| NDA Lots (3) Completed | | 7/2000 | | 01/2001 |
| Completion of 1 Year Stability for NDA | | 8/2001 | | 8/2001 |
| Formulation Peer Review | | 11/2002 | | |

Drug Substance**Plan Date:**

| Activity | KG | Plan | Actual | Actual Projected Cost/kg |
|----------|----|------|--------|--------------------------|
|----------|----|------|--------|--------------------------|

See the Following page for a summary of Bulk Drug deliveries in SPD.

Toxicology**Plan Date: 12/98**

| Toxicology Activity | | Plan Start ??Date?? | Actual Start Date | Report Completed |
|------------------------------|--|---------------------|-------------------|------------------|
| 2-week oral Rat/Monkey | | 7/1997 | 6/1997 | 9/1998 |
| Acute Studies | | 8/1997 | 8/1997 | 12/1997 |
| Mouse Lymphoma/Micronucleus | | 11/1997 | 11/1997 | 4/1998 |
| 1 Month Rat/Monkey | | 12/1997 | 12/1997 | 12/1998 |
| Pregnant Rat/Rabbit RF | | 1/1998 | 1/1998 | 11/1998 |
| SEG II Rat/Rabbit | | 3/1998 | 3/1998 | 2/1999 |
| Guinea pig sensitization | | 11/1998 | 11/1998 | 2/1999 |
| 3 Month oral Rat/Monkey | | 9/1999 | 10/8/1999 | 8/2000 |
| Seg VIII Rat | | 9/1999 | 10/8/1999 | 12/2001 |
| IV Irritation studies, set 1 | | 7/1999 | 7/15/1999 | 8/1999 |
| IV Irritation studies, set 2 | | 2/2000 | 2/2000 | 3/2000 |
| IV 2-week Rat/Monkey Studies | | 6/2000 | 6/2000 | 01/2001 |
| Neonatal/Juvenile Rat | | 10/1999 | 11/1999 | 7/2000 |

* Target cost of drug substance at launch is \$2,500/kg (Finished Product)

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| SPD ABT-773 Bulk Drug Deliveries Update | | | | | | |
|-----------------------------------------|-------------|--------|---------------|-------------------|--------------|----------------------|
| | Target Date | Amount | Delivery Date | Amount | Lot # | Amount after milling |
| Campaign 1 | 2/28/99 | 200 Kg | 2/23/99 | 209 Kg | 50-007-CA-00 | 207.5 Kg (2/26)* |
| Campaign 2a | 6/15/99 | 140 Kg | 6/17/99 | 131 Kg | 54-702-NI-00 | 129.4 Kg (6/19)* |
| Campaign 2b | 7/15/99 | 140 Kg | 7/21/99 | 121.5 Kg | 55-208-CB-00 | 119.3 Kg (8/4)* |
| Tox lot | 8/30/99 | 5 Kg | 8/25/99 | 6.1 Kg | 55-718-NI-00 | |
| Campaign 3a | 9/30/99 | 160 Kg | 10/8/99 | 170.5 Kg | 58493CB00 | 138.4 Kg (10/16)* |
| Campaign 3b | 10/21/99 | 160 Kg | 10/11/99 | 176.5 Kg | 58494CB00 | 169.5 Kg (10/16)* |
| Pilot run 1 | ----- | 15 Kg | 10/30/99 | 18.9 Kg | 59763N100 | no milling |
| Pilot run 2 | ----- | 15 Kg | 2/5/00 | 15.5 Kg | 61790NI00 | no milling |
| Pilot run 3 | ----- | 25 Kg | 1/30/00 | 27.5 Kg | 62764CB00 | 27.3 Kg (4/18)* |
| Campaign 4 | 12/10/99 | 320 Kg | 11/23/99 | 355 Kg | 61741CB00 | 309 Kg (3/2)* |
| Campaign 5 | 12/30/99 | 300 kg | 12/16/99 | 300.5 Kg | 60665CB00 | 269.2 Kg (3/3)* |
| Campaign 6 | 2/28/00 | 280 Kg | 2/23/00 | 321 Kg | 62796CB00 | 315.5 Kg (3/6)* |
| Campaign 6 (IV) | 2/28/00 | 15 Kg | 2/22/00 | 20 Kg | 62797CB00 | 18 Kg (3/15)* |
| Campaign 7 | 3/30/00 | 300 Kg | 4/10/00 | 370 Kg | 63890CB00 | 361.2 Kg (4/18)* |
| Campaign 7 (IV) | 3/30/00 | 5 Kg | 3/29/00 | 19 Kg | 63889CB00 | 17.2 Kg (4/11)* |
| Campaign 8 | 4/25/00 | 200 Kg | 5/11/00 | 263 Kg | 64970CB00 | 256.5 Kg (5/15) |
| Campaign 8 (IV) | 4/25/00 | 15 Kg | 4/25/00 | 19.8 Kg | 64971CB00 | 17.7 Kg (5/11)* |
| Campaign 9 | 6/15/00 | 300 Kg | 6/14/00 | 375.7 Kg | 65064CB00 | 355.7 Kg (6/20/00) |
| Campaign 9 (IV) | 6/15/00 | 15 Kg | 6/5/00 | 18.1 Kg | 65065CB00 | 16.7 Kg (6/9/00)* |
| Campaign 10 | 7/15/00 | 300 Kg | 7/26/00 | 361.2 Kg | 67176CB00 | 359.0 Kg (8/10/00) |
| Campaign 11 | 8/15/00 | 300 Kg | 8/4/00 | 333.7 Kg | 68285CB00 | 271.9 Kg (9/7/00) |
| Campaign 12 | 10/6/00 | 300 Kg | 9/27/00 | 356 Kg | 69458CB00 | 292.3 Kg (12/8/00) |
| Campaign 13 | 11/23/00 | 300 Kg | 11/15/00 | 351.2 Kg | 71665CB00 | 349.1 Kg (12/20/00) |
| | | | | Total (year 2000) | 2,815.5 Kg | |
| Campaign 14 | 1/28/01 | 300 Kg | 1/26/01 | 327.5 Kg | 73886CB00 | 318.9 Kg (02/13/01) |
| Campaign 15 | 2/10/01 | 330 Kg | 1/14/01 | 354.9 Kg | 71699CB00 | 353.8 Kg (02/02/01) |

* Weight after rework

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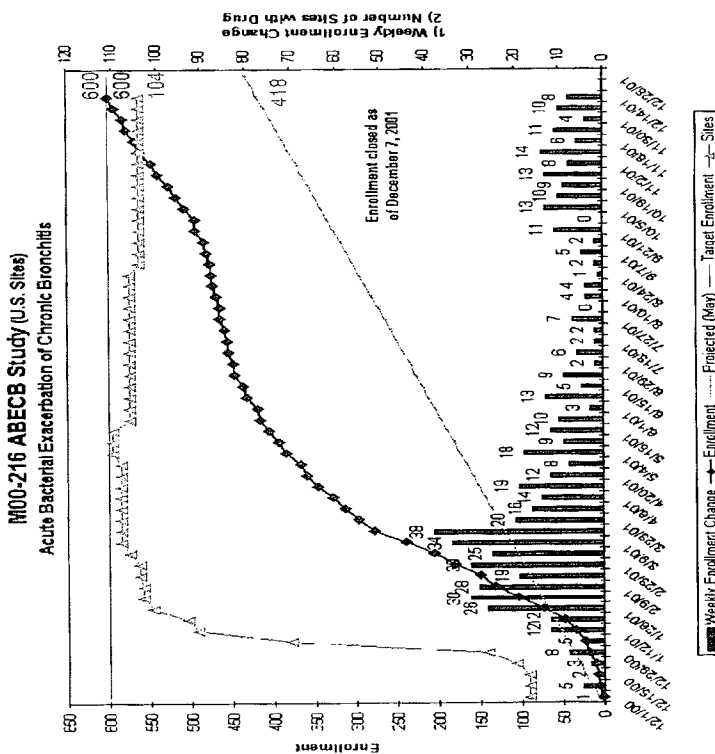
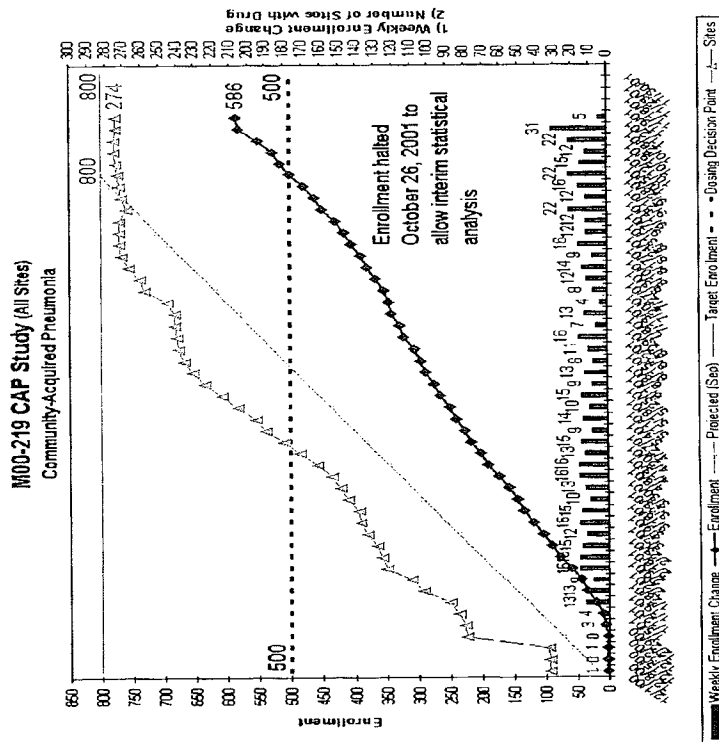
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March 2002**ABT-773****Ongoing Clinical Studies** (List first time in man, Phase II Dose-Ranging and Pivotal Trials)

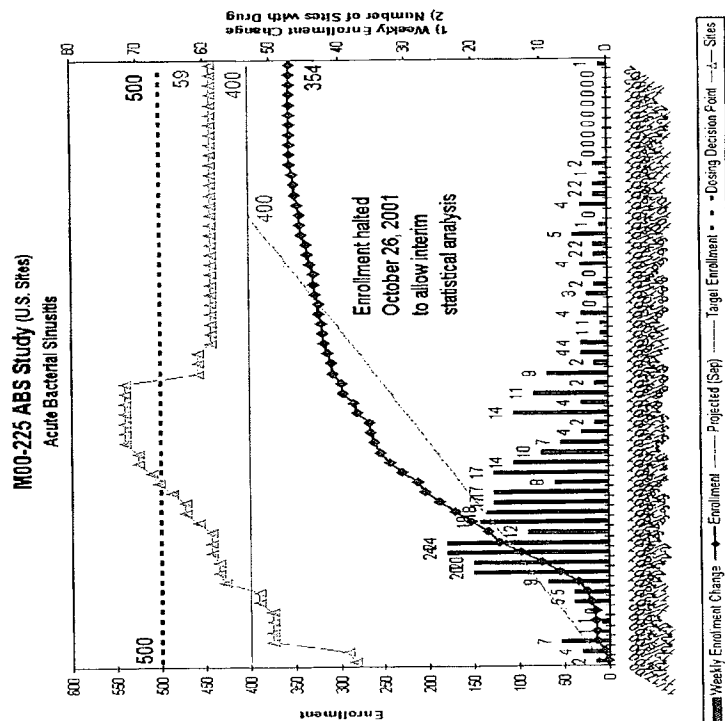
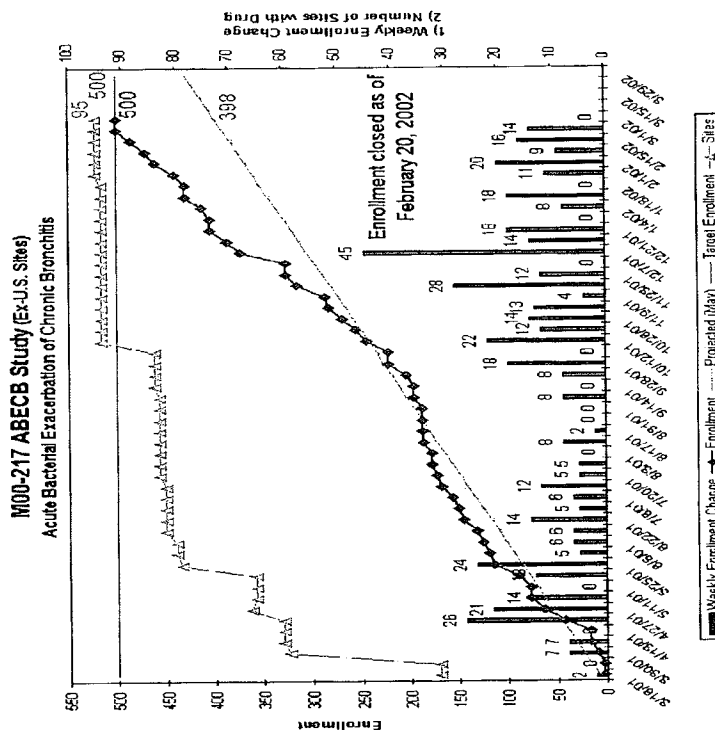
| | | |
|---------------------------|-----------------------------------|--------------------------------------------------|
| Protocol: | M00-219 – Dose-Ranging CAP | M00-216 – Phase III ABECB vs Azithromycin |
| Objective: | Dose selection. | Safety & Efficacy |
| ABT-773 Doses: | 150mg QD vs 150mg BID, 10 days | 150mg QD, 5 days |
| Comparator Doses: | None | Azithromycin 500mg day 1, 250mg QD for 4 days |
| Target Enrollment: | 600 | 600 |
| Status: | Completed enrollment. | Completed enrollment |
| Major Findings: | | |

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March 2002**ABT-773****Ongoing Clinical Studies** (List first time in man, Phase II Dose-Ranging and Pivotal Trials)**Protocol:****Objective:** Safety & Efficacy**ABT-773 Doses:****Comparator Doses:** Levofloxacin 500mg QD for 7 days**Target Enrollment:****Status:****Major Findings:****M00-217 - Phase III ABECB vs Levofloxacin**

Dose Selection
150mg QD vs 150mg BID, 10 days
None
600
Completed enrollment



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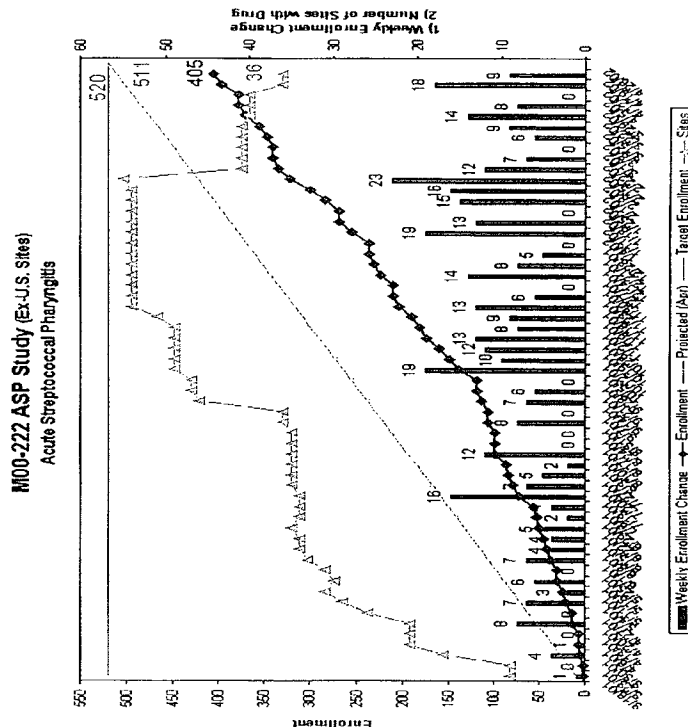
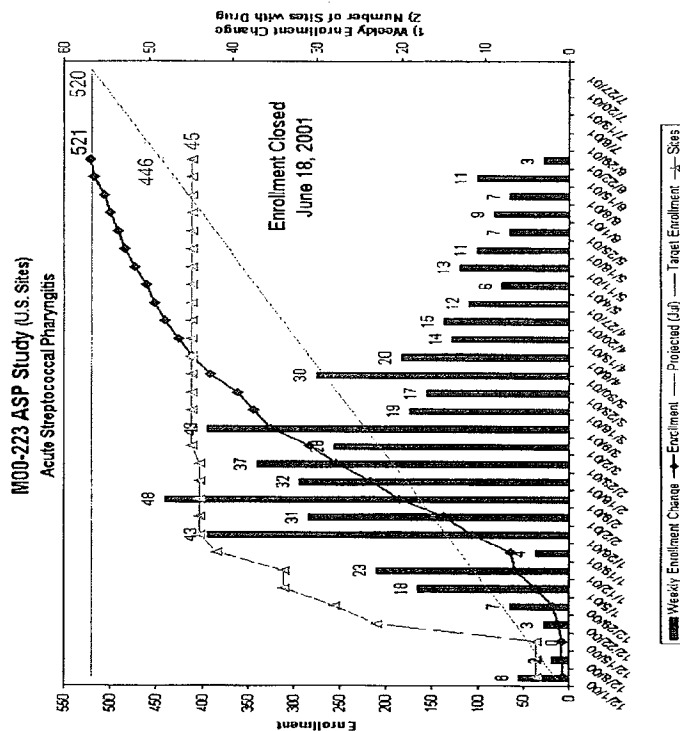
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Ongoing Clinical Studies (List first time in man, Phase II Dose-Ranging and Pivotal Trials)

| | |
|--------------------|---------------------------------------------------------|
| Protocol: | M00-223 - Phase III Pharyngitis vs Penicillin 500mg TID |
| Objective: | Safety & Efficacy |
| ABT-773 Doses: | 150mg QD., 5days |
| Comparator Doses: | Penicillin 500 mg TID, 10 days |
| Target Enrollment: | 520 |
| Status: | Completed enrollment |
| Major Findings: | |



CERTIFICATE OF SERVICE

I hereby certify that this document(s) filed through the ECF system will be sent electronically to the registered participants as identified on the Notice of Electronic Filing (NEF) and paper copies will be sent to those indicated as non registered participants on February 18, 2008.

Date: February 18, 2008.

/s/ Eric J. Lorenzini

Eric J. Lorenzini (*pro hac vice*)